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1. Thorn, G. W.: *J. Mt. Sinai Hosp.*, March-April 1942.
2. Loeb, R. F.: *J. A. M. A.*, May 31, 1941.

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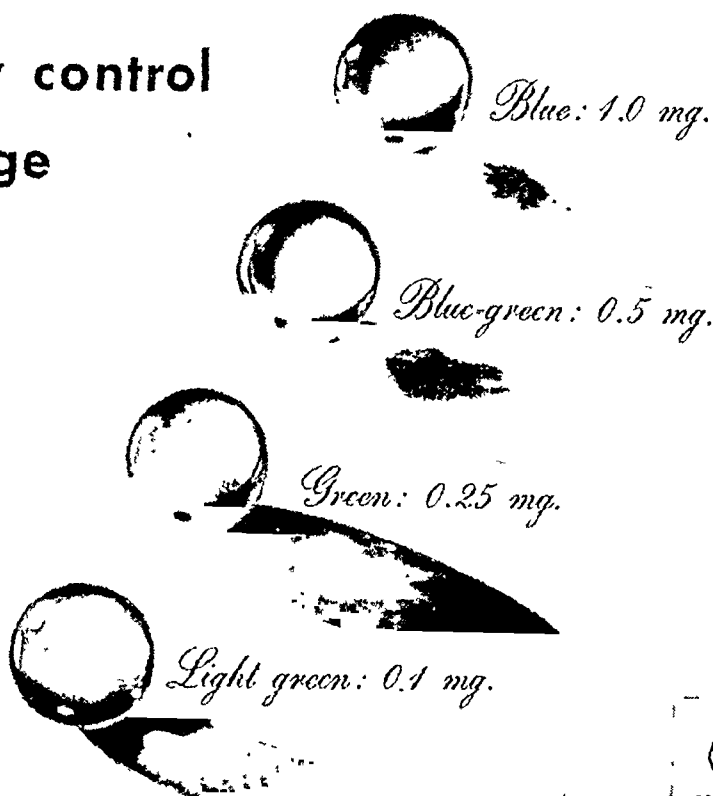


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# The Journal of CLINICAL ENDOCRINOLOGY

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## Metabolic Effects of Testosterone Propionate in Addison's Disease<sup>1, 2</sup>

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WHEN TESTOSTERONE propionate is given intramuscularly to man there occurs regularly a depression in the urinary excretion of nitrogen, inorganic phosphorus, sulfate, sodium, potassium and chloride and a gain in body weight due chiefly to water retained in association with salts and protein. This pattern of response varies little over a wide range of subjects tested including hypogonad men (1, 2, 3, 4) and women (4), normal men (2, 5) and women (2), aged men (6, 7) and the immature boy (8). In Cushing's syndrome in women (9) and in the aged man with osteoporosis (7) calcium is retained with nitrogen and phosphorus. This may not be peculiar to these conditions, however, and more protracted study of other subjects may

well demonstrate the same process. The rise in basal heat production with testosterone propionate has thus far been well seen only in eunuchoids (1, 3, 10) but the protracted treatment necessary to establish an indubitable change has not been undertaken in others. Creatine excretion, when substantial or when sustained by creatine ingestion, may be depressed by testosterone propionate in the eunuchoid (1, 4), in the pubertal boy (8), and in the hypogonad woman (4) but the creatine tolerance of young boys (11) and normal men (12) has been reported to be uninfluenced. With this exception the state of gonadal function or the age of the subject seems to make relatively little qualitative difference in those metabolic responses to testosterone propionate which have been examined in sufficient detail. Other glands of internal secretion, however, may conceivably be intermediaries in these reactions.

The striking analogies between the sodium and chloride retaining properties of the sex hormones and of several steroids of the adrenal

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<sup>1</sup> This investigation was supported by a grant from the Committee on Research in Endocrinology of the National Research Council

<sup>2</sup> The testosterone propionate (Oreton) and desoxycorticosterone acetate (Cortate) were generously provided by Drs Erwin Schwenk and Max Gilbert of the Schering Corporation, Bloomfield, N J

series (5, 13) at once suggest that testosterone may act through the adrenal cortex. The association of retention of nitrogen, inorganic phosphorus and potassium with that of sodium chloride and water in the testosterone effect, however, is unlike any known reaction to an adrenal steroid. The disposition of adrenal extracts and desoxycorticosterone to promote potassium diuresis at once comes to mind as an illustration. Such a substance as corticosterone may induce nitrogen loss, apparently in the course of promotion of gluconeogenesis (14). The effect of some chemically unknown adrenal agent however may more nearly approximate that of testosterone. The general body growth and enhanced muscular development of the childish victims of adrenal cortical hyperplasia correspond to those seen in boys with interstitial cell tumors of the testis and bespeak anabolic influences from the adrenal not unlike those exerted by testosterone. It is not known whether the normal adrenal secretes such an agent.

In this account we have attempted to assess the importance of the adrenal cortex as an intermediary organ in the metabolic response to testosterone propionate by study of a man and a woman with Addison's disease. The subjects were maintained in good condition with added salt and desoxycorticosterone acetate. While we have no autopsy proof of complete absence of effective adrenal tissue in these people, it is clear that these glands were too imperfect to sustain sufficient secretion in response to the usual physiologic stimuli playing upon them. This does not exclude a conceivable reaction of residual tissue to the administered androgen but creates a presumption against it.

METHODS

The subjects were studied in the metabolism unit of the hospital where they received constant diets of sufficient caloric value to maintain body weight on schedules of limited and fairly regular activity. Each subject received sodium chloride supplements and 1 to 1.25 mg. of desoxycorticosterone acetate in sesame oil, intramuscularly, daily. They were in good condition throughout the experiments. The methods of dietary control and the techniques of chemical analysis of urine and blood and

measurements of respiratory metabolism were the same as in our previous work (2, 3, 4) and need not be repeated here.

PROTOCOLS

T. K., was a 39-year-old man, a patient of Doctor Martin Goldner and H. T. Ricketts who kindly permitted these studies. He was first seen in August 1941, suffering from fatigue, loss of weight (20 lb.), difficulty in walking and recurrent attacks of nausea and vomiting for 2 years. His skin was diffusely darkened, with intensification about the genitalia. The gums and buccal mucosa were pigmented. His blood pressure was 100/74 mm. Hg. The serum sodium was 126 and 120 milli-equivalents per liter, chloride 90 m eq. per liter, potassium 5.3 and 5.7 m. eq. per liter. Urea nitrogen was 25 and 30 mg. per cent, non-protein nitrogen 42 mg. per cent. Roentgen-ray examination showed no evidence of pulmonary tuberculosis and no evidence of calcification of the adrenal glands. The testes, phallus and prostate glands were somewhat small in size.

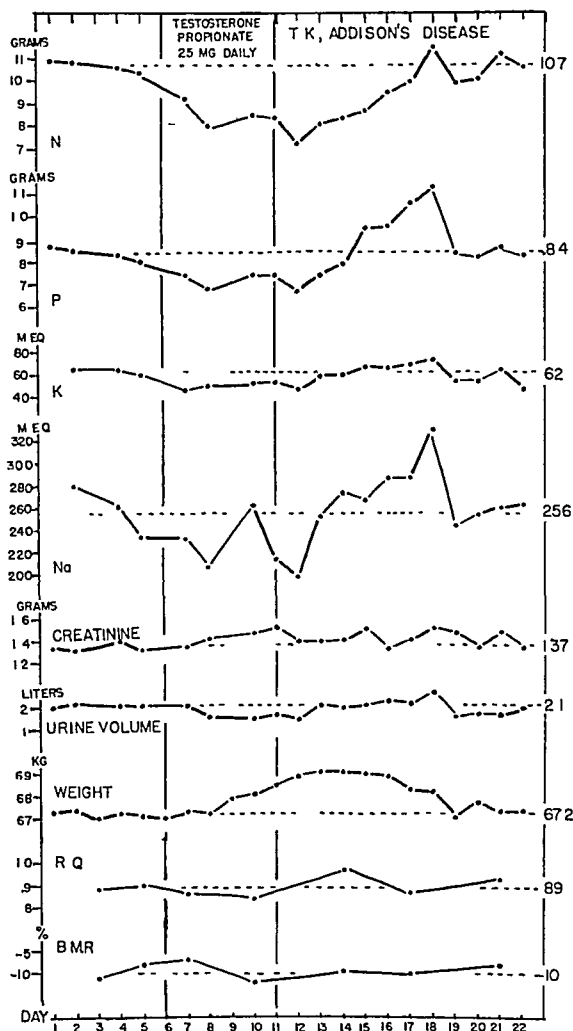
The Addison's disease was complicated by posterior lateral sclerosis of the spinal cord with involvement of the lower extremities which were spastic with increased tendon reflexes, positive Babinski signs, ataxia and diminished vibration sense (Dr. R. B. Richter). Bilateral pes cavus was present. Roentgenograms showed multiple congenital anomalies of the lumbo-sacral region including failure of fusion of the posterior segments of lumbar 5 and sacral 1 with partial lumbarization.

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE, 25 MG. DAILY, ON SEVERAL BLOOD CONSTITUENTS OF A MAN (T. K.) AND WOMAN (P. K.) WITH ADDISON'S DISEASE

Day	Hematocrit vol. %	Blood urea N mg. %	Serum Na m.eq./liter	Serum Cl m.eq./liter	Serum K m.eq./liter
T. K.					
1		15.0	136.0	101.0	4.75
4		14.6	135.7	100.6	3.75
6		15.1	138.8	100.3	4.35
11		11.7	143.8	104.7	4.20
13		9.3	140.4	102.3	4.60
20		13.8	142.5	101.8	4.20
P. K.					
1	39	13.3	139.3	106.1	4.95
8	37	12.9	143.3	106.7	5.05
10	36	9.6	141.4	105.0	4.38
14	35	9.5	141.6	102.6	4.70
16	37	10.1	139.5	103.7	4.63
23		13.3	138.1	102.1	4.45

The androgen was given intramuscularly from day 6 through day 11 in T. K. and from day 8 through day 13 in P. K. Enumeration of days as given in figure 1 and 2.

FIG 1 Effect of testosterone propionate on several urinary constituents, body weight, respiratory quotient and basal metabolic rate of the man (T K) with Addison's disease. The subject was maintained in good condition with salt supplements and 1 mg. of desoxycorticosterone acetate daily. The dotted lines and the figures to the right thereof signify pre-treatment baselines.



tion of the first sacral segment. Myelography with an opaque medium at a later date showed no lesion of the spinal canal. The spinal fluid was normal and Wassermann and Kahn tests on the serum were negative. There was no hematologic evidence of pernicious anemia and free acid was found in the stomach after administration of histamine.

In the interval between the first admission in August, 1941, and March, 1942, he was maintained in fair to good general condition on desoxycorticosterone

acetate by injection with little or no supplementary salt. Toward the end of this period he took 2.5 mg. of desoxycorticosterone acetate daily and was troubled by occasional edema of the ankles.

In March, 1942, his response to testosterone propionate was studied. For this purpose he was placed upon a diet of C 247, P 71, F 112, Cal 2280, yielding an estimated 11.4 gm N, 1.76 gm P, 0.96 gm S, 1.50 gm Na, 3.39 gm K. To this was added 12 gm of NaCl daily at the table. Fluid intake (2500 cc daily), includ

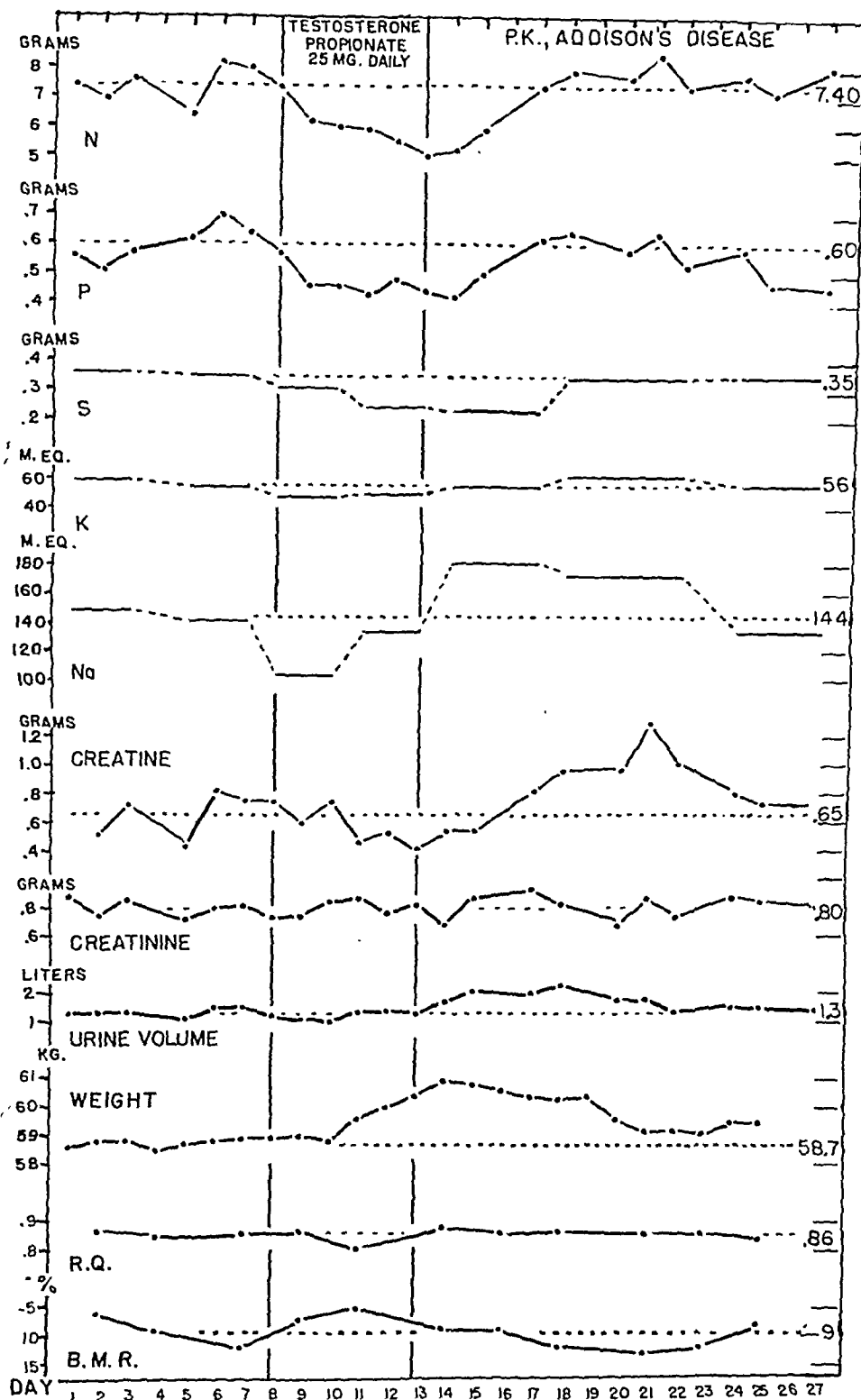


FIG. 2. Effect of testosterone propionate on several urinary constituents, body weight, respiratory quotient and basal metabolic rate of the woman (P. K.) with Addison's disease. The subject was maintained in good condition with salt supplements and 1.25 mg. of desoxycorticosterone acetate daily; 1.32 gm. of creatine hydrate was ingested daily. The dotted lines and the figures to the right thereof signify pretreatment baselines.

ing distilled drinking water, was kept constant in amount and composition. He received 1 mg. of desoxycorticosterone acetate daily intramuscularly. On this regimen he remained in good condition. His blood pressure ranged from 90/68 to 122/82, averaging in the neighborhood of 106/76 mm. Hg. The serum electrolytes and blood urea nitrogen, as seen in table 1 were normal. In the two weeks preceding treatment with testosterone propionate, 7 measurements of respira-

tory metabolism gave an average B.M.R. of -9 and an average basal heat production of 1539 Calories per day. Twenty-five mg. of testosterone propionate was given intramuscularly in sesame oil daily from April 16 through April 21. The data are recorded in figure and table 1.

P. K. was a 39-year-old woman referred to us by Dr. E. C. Wrightsman. She was first seen in August

1939, complaining of soreness of the tongue, recurrent vesicular lesions of the buccal mucosa for one year darkening of the skin, faintness on rising in the morning, weakness for 3 months and loss of 19 lb of weight in the preceding two months. She was deeply pigmented there being a generalized browning of the skin with numerous smudges of deeper hue distributed over the face, neck, elbows, knees and backs of the hands with strong brown markings in the lines of the palms. There were numerous dark freckles especially on the forearms and sides of the neck. The mucosa of the lips was darkened and there were a few patches of pigment on the buccal mucosa and gum margins with darkish streaks on the tongue. The few aphthae on the buccal mucosa were not attributable to Addison's disease, nor was the history of the sore tongue. Her blood pressure was 116/58 mm Hg the systolic pressure declining 20 points on standing while the diastolic pressure remained unaffected. The serum sodium was then 137 m eq per liter, chloride 102, potassium 4.95. There was no elevation of the blood urea nitrogen. There were calcified lesions in the right apex in the midportion of the right lung field and at the hila but no evidence of active tuberculosis. There was no evidence of calcification in the adrenal area. Menses were normal.

In the ensuing 3 years the patient has on the whole done well on moderate salt supplements and injections of desoxycorticosterone acetate. There have been bouts of nausea and vomiting and on one occasion, in association with a severe upper respiratory infection, she required emergency measures. On another occasion nausea, vomiting and collapse followed discontinuance of medication and an irregular schedule of living necessitated by the illness of her husband. Her blood pressure at one time reached 80/65 but has usually ranged about 110/72 mm Hg. The serum sodium at one time was 128 m eq per liter but was usually normal. Previous to these studies she was taking 1.25 mg of desoxycorticosterone acetate intramuscularly daily and about 3 gm of supplementary salt.

In May, 1942 her response to testosterone propionate was studied. For this she was placed upon a diet of carbohydrate 238, protein 60, fat 94, calories 2039, yielding an estimated 9.6 gm N, 1.16 gm P, 0.77 gm S, 3.30 gm K, 0.82 gm Na. To this 4 gm of NaCl was added at the table and 6 gm of NaCl given in a flavored drink. Her fluid intake including distilled drinking water was kept constant in amount (2100 cc daily) and in composition, 132 gm of creatine hydrate was given daily. She received 1.25 gm of desoxycorticosterone daily, intramuscularly. She remained in excellent condition the blood pressure ranging from 104/72 to 114/84 mm Hg. The serum electrolytes as given in table 1 were normal. In the 2 weeks preceding treatment with testosterone propionate 6 measurements of respiratory metabolism gave an average B.M.R. of  $-7$ , and an average basal heat production of 1250 Calories. Twenty-five mg of testosterone propionate was given daily from June 9 through June 14. The data are presented in figures 2 and table 1.

## DISCUSSION

The pattern of response to testosterone propionate of the affected urinary constituents in a man (*T K*) and a woman (*P K*) with Addison's disease corresponds closely to that previously given for normal and hypogonadal men and women. The depression in urinary nitrogen excretion begins promptly in both subjects, is well sustained for the duration of treatment and disappears slowly during the recovery phase of the experiment without conspicuous loss of the retained material in the time studied. The amount of nitrogen retained per kg of original body weight per day at the time of sustained maximum effect is 0.43 gm in the man and 0.39 gm in the woman. This approximates values for normal young men and women (2) and aged men (6) and is somewhat less than the responses given by hypogonadal men (2) and the one hypogonadal woman studied (4). Urinary inorganic phosphorus declined sharply in both subjects during treatment. The discharge of the retained phosphorus during the recovery period in *T K* is not unique and was previously observed in an aged man (*M L*) with intact adrenals (6). A decline in urinary sulfate was seen in *P K* (fig 2, table 2) during treatment. Urinary potassium declined in both subjects although the effects were more distinct in *T K*. Although irregularities in urinary sodium excretion in *T K* somewhat mar the data, the conspicuous salt retention in both subjects under the influence of testosterone propionate was manifest and the loss of this retained salt was complete early in the recovery phase. This is the usual course of events in those with intact adrenals, diuresis occurring while vestiges of nitrogen retention remain. The salt and water retention further exemplified by the rapid weight gains is more prominent here than in other subjects. This difference may be accounted for by the higher salt intake of the patients with Addison's disease rather than by endocrinologic peculiarities. The spontaneous creatinuria of *T K* was too slight to permit definition of a testosterone effect and the data are not given. In *P K*, however, creatinuria was sustained at a high level by creatine ingestion and the usual depressing influence of the androgen was more distinct. In neither instance was creatinine excretion altered.

Basal heat production and the fasting respiratory quotients of the patients with Addison's disease were as little modified by testosterone propionate as in those with intact adrenals studied in experiments of this duration (2). It should be stressed once more that the calorogenic properties of testosterone propionate observed in the eunuchoid often require several weeks for unmistakable demonstration (3).

The concentrations of sodium, potassium and chloride in the serum of the patients with Addison's disease were unaffected by testosterone propionate (table 1) despite the retention of these minerals. No significant hemodilution as judged by hematocrit occurred in *P. K.* The depression of the concentration of urea nitrogen in both subjects is in all probability significant as it has been observed repeatedly before during treatment with this androgen. It is to be interpreted, we believe, as a reflection of the reduction in protein catabolism under the influence of testosterone propionate.

There is thus no reason adduced here for believing that testosterone propionate exerts any of its metabolic effects indirectly through the adrenal cortex. It is quite possible, of course, that adrenal cortical function may be necessary for testosterone response in the sense that tissue deprived of adrenal hormones may react poorly. Since our subjects were kept in good condition with added salt and small amounts of desoxycorticosterone acetate we can make no comments on this latter point and pertinent experiments would be difficult of execution in man. It may be recalled that several of the metabolic effects of testosterone propionate were likewise well manifested in a eunuchoid suffering from a supra-sellar cyst, shown at autopsy to have largely destroyed the pituitary gland (1), and in dwarfs with multiple physiologic evidence of hypopituitarism (15). The nitrogen-retaining action of methyl testosterone was demonstrated in dwarfs with hypopituitarism and both the calorogenic properties of this androgen and the enhancement of creatinuria were demonstrated in a cretin (16). Thus far no other gland of internal secretion has been shown to be an obligatory intermediary organ in metabolic reactions to androgens in man. Corroboration from animal ex-

periments in which participation of remnant tissue can be more readily excluded will be awaited with interest.

#### SUMMARY

A man and a woman with Addison's disease maintained in good condition by salt supplements and by daily injections of desoxycorticosterone acetate were given testosterone propionate intramuscularly, 25 mg. daily. The characteristic metabolic effects of the androgen including depression of urinary nitrogen, inorganic phosphorus, sulfate, sodium, potassium and creatine, with gains in body weight were well seen. The basal metabolic rates, fasting respiratory quotients and concentrations of serum electrolytes were unaltered within the time studied. No reason was adduced for supposing that the adrenal cortex is a necessary intermediary in the metabolic response to testosterone propionate in man.

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# Addison's Disease in a Seven-Year-Old Boy<sup>1</sup>

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CASE REPORTS of classical Addison's disease in children are infrequent Atkinson (1), reviewing the literature up to 1937, found 40 cases which he believed could be interpreted as adrenal insufficiency Only 5 of these occurred in children under 10 years of age Since that time, there have been 5 additional cases noted in the literature Three of these have been classified in the syndrome of adrenal insufficiency associated with macrogenitosomia (Butler et al , 2, Thelander and Cholfin, 3, Wilkins et al , 4) Anderson (5) in 1942 reported the case of an 11-year old boy with primary Addison's disease which he believed was the result of primary atrophy of the adrenals Renshaw and Manning (6) observed a 12 year old boy who, at autopsy, proved to have tuberculosis of the adrenals

Recently we have had under observation a 7 year old boy with adreno cortical insufficiency, whose case report should perhaps be added to the growing literature on this subject Although the etiology is not definite, it is felt that the picture presented by the patient may be the result of primary or post infectious atrophy of the adrenal glands

## CASE REPORT

G E, a 7 year old white male was admitted to the Communicable Disease Unit of the Los Angeles County Hospital on Aug 11, 1942 with the complaint of stupor and sleepiness for 4 days

Two and one half months prior to admission, the patient's parents first noticed that his skin was becoming tan, apparently not related to sun exposure Con-

comitantly, he developed marked enuresis, lost weight and fatigued readily at play This condition continued until 5 days before his entry to the hospital when he began to vomit everything eaten and gradually became stuporous, for which he was brought to the hospital On the day before admission he complained of headache and cramps in his legs

The history revealed that when the patient was 2 years old he suffered a severe attack of 'pneumonia' which ran a course of 10 weeks, during which period he maintained a 'high fever' of from 4 to 5 weeks At the height of his illness, numerous 'hemorrhages' of varying size appeared 'under' the skin and the boy 'bled from the mouth' Subsequently, the hemorrhagic areas cleared, leaving a skin of normal appearance Two years prior to his present admission, the patient had 'severe' chicken pox, with 'high fever' present for 5 weeks There appeared to be no sequelae to either illness except frequent periodic attacks of vomiting, related to upper respiratory infections At the age of 6, one year before coming under our observation, he had measles and pertussis, the latter lasting 6 weeks and being again aggravated by 'high fever' The degree of fever in all instances was not known by the parents

The patient was a full term normal infant, weighing 8 pounds at birth and delivered spontaneously He was breast fed for the first 13 months, after which he was maintained on a regular feeding schedule and never became a feeding problem Orange juice and cod liver oil were added to his diet early and in adequate dosage At the age of 6 months he sat alone, while at the age of one year he began to walk He did not talk in complete sentences until after the age of 2 1/2 years His first tooth did not erupt until after the age of one year with the exact date not known There is no history of immunization procedures

As a younger child, the boy was always quiet and did not associate freely with other children However, he was active and apparently enjoyed playing by himself His appetite has always been good and his dietary habits have not been unusual except that during the last few years, and especially in the last year, he manifested a marked fondness for salted crackers, sauer kraut and dill pickles, preferring these to candy

Enuresis had been present almost all of his life This disturbance became more severe after the previously mentioned pneumonia and was especially severe

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<sup>1</sup> This patient was observed in the Los Angeles General Hospital Endocrine Clinic under the direction of Dr E Kost Shelton Associate Professor of Medicine University of Southern California whose observations and comments were deeply appreciated by the authors



before the present illness which precipitated his admission to the hospital.

The family history is not particularly informative. His parents, both 31 years of age, denied venereal disease, tuberculosis, epilepsy and all other significant diseases. Recent contacts with contagious disease and tuberculosis on the part of the patient were denied by both. Two siblings, a brother, age 9, and a sister, age 6 years, are living and well. The mother has had no other pregnancies.

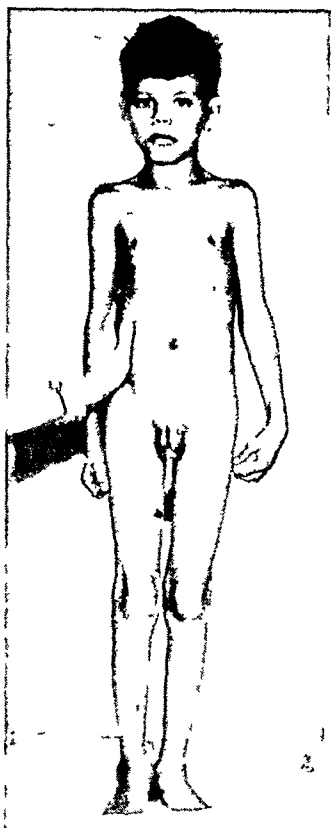


FIG. 1. G. E., age 7. Addison's disease. Note contrasts of color in nurse's skin and that of the patient

On admission, the patient's temperature was 100.8°F. by rectum, pulse 138 per minute, respiration, 18, and blood pressure 60/30 mm. Hg. He was a thin, tall, markedly dehydrated white boy of the stated age of 7, in no acute distress but stuporous and apathetic. He lay quietly in bed and was co-operative. A deep brownish pigmentation of the skin was noted as being present over the entire body with an accentuation in the folds and creases. His pupils were regular and equal and reacted to light and in accommodation; there was no nystagmus and extra-ocular movements were normal. The tongue and buccal mucosa were dry. The lips and palatal mucosa presented small discrete spots of deep brownish-purple pigmentation. Passive motion of the neck revealed moderate stiffness in few degrees of anterior flexion. Results of examination of the heart and lungs were negative. The patient was scaphoid and there was moderate

tenderness in the right lower quadrant which subsequently was not noticed. There were no palpable masses in the abdomen. The genitalia were normal in all respects except for slightly increased pigmentation. All deep reflexes were hypoactive but equal and the superficial reflexes were present and equal. There was a doubtful Brudzinski sign and a suggestive Kernig sign bilaterally.

Initial laboratory work disclosed a 75 per cent hemoglobin (Sahli), 4,660,000 erythrocytes and 5,000 white blood cells with 70 per cent polymorphonuclear cells and 30 per cent mononuclears; abnormal forms were not identified. The urine analysis was negative for sugar, albumin and by microscopic examination. The blood Wassermann and Kahn reactions were negative. Spinal fluid examination resulted in a bloody tap with the 6 cc. of grossly bloody fluid containing 33 cells, 100 per cent of which were mononuclears. The pressure was under 50; Pandy test was two plus positive; and spinal chlorides were 650 mg. per cent. On culture no bacteria or acid-fast bacilli could be found. The blood chloride level at this time was 436 mg. per cent, sodium 320 mg. per cent, and potassium 32 mg. per cent. One week after admission, another spinal fluid examination revealed 10 cc. of xanthochromic fluid with a sediment containing many erythrocytes and an occasional lymphocyte. Pandy test was still two plus positive while the chlorides were now 670 mg. per cent. Culture for bacteria and acid-fast bacilli was again negative.

Two weeks after admission, the patient was transferred to the pediatric ward, service of Dr. Milk Brooks. There, with the boy asymptomatic and under treatment, a repeated spinal fluid examination was completely normal with the chlorides over 700 mg. per cent and a culture again negative for all bacteria, including acid-fast bacilli. At this time the blood sodium was 292 mg. per cent, icteric index 7, and albumin-globulin ratio 4.9-2.1. The basal metabolic rate was minus 27. A glucose tolerance test, by standard method, revealed the following levels expressed as mg. per cent: fasting, 80; first hour, lost; second hour, 100; third hour, 103; fourth hour, 100; and fifth hour, 69.

Roentgenograms of the chest on two occasions did not reveal any abnormal findings. Flat film of the abdomen revealed the renal contours to be within normal limits, the psoas shadows appeared normal, and there was no evidence of calcification in the suprarenal areas. A lateral film of the skull demonstrated a normal sella turcica with no evident intracranial pathological changes.

Ophthalmoscopic examination revealed normal fundi and refraction demonstrated normal vision. Punch biopsy of the skin demonstrated increased pigmentation of the basal cell layer.

At the time of admission, prompt relief from his symptoms followed the administration of adrenal cortical extract, intravenous salt and glucose. During his hospitalization the patient's course was characterized by frequent acute exacerbations of apathy, stupor, asthenia, nausea and vomiting, all associated with dis-

continuation of therapy as above. With the use of intramuscular adrenal cortical extract and adequate salt orally (parenterally in severe exacerbations), remissions invariably resulted with the boy becoming alert and manifesting a desire to play. No spontaneous emissions were noted. Evidence of meningeal irritation gradually cleared after his entrance to the hospital, and all such signs were absent on admission to the pediatric ward.

In view of the very strong probability that the patient was suffering from true Addison's disease, he was placed on a Cutler-Power-Wilder (7) regime with the diet as recommended and the withholding of all therapy for several days. However, on the day before the urine samples were to be collected, the boy lapsed into a severe crisis with profound asthenia and marked vomiting. Large doses of intravenous adrenal cortical extract (40 cc.), physiological saline solution, glucose and sodium citrate were necessary to evoke a emission at this time. Within 24 hours vomiting ceased and the patient's weakness and apathy had disappeared. In view of this crisis no further salt restriction tests were attempted. One week after this episode, with the patient receiving 10 cc. of adrenal cortical extract intramuscularly daily, and a diet high in glucose and salt, the blood chemistry revealed an NPN of 33, chlorides of 528, with sodium of 314 and potassium 28 mg. per cent.

Subsequently, the patient was given desoxycorticosterone, 5 mg. daily, but received this only 3 days, before being removed from the hospital at this time because of his family's urgent desire to return to their home in Kansas. On the day of discharge, blood studies disclosed an NPN of 31, chlorides of 500, with sodium of 302 and potassium of 19.1 mg. per cent. At this time he packed cell volume was 31 mm., plasma volume 69 and corrected sedimentation rate 3 mm. per hour. The hemoglobin was now 62 per cent; 3,340,000 erythrocytes, and 4,700 white blood cells with a differential count of 56 per cent lymphocytes, 32 per cent neutrophils, 12 per cent stabbs, no monocytes, eosinophils or basophils. Reactions for the Mantoux test in concentration up to and including 0.1 mg. were all negative.

The boy's medication consisted primarily of the natural adrenal cortex hormone and later desoxycorticosterone, with a moderately high carbohydrate diet and additional sodium chloride orally, except on those occasions when crises demanded intravenous therapy.

#### DISCUSSION

The etiology of the Addisonian picture presented by this boy must remain hypothetical. Although it is generally conceded that the disease in the majority of such patients, both adults and children, is of tuberculous origin, this disease was never proven in the patient. The negative response to the Mantoux test on two occasions and the normal chest film mitigates heavily against such a diagnosis.

The early history, which we have emphasized, of 'hemorrhagic' complications during the pneumonia episode, and subsequent stormy illnesses of varicella and pertussis with high temperatures, offers a probable and ready explanation for adrenal atrophy. The adrenal gland is susceptible to degenerative, hemorrhagic or inflammatory changes, such as may have occurred in the above disorders. It is becoming more apparent that the incidence of atrophy of the adrenals is more frequent than has been generally accepted. Susman (8), for example, reviewed the literature and found 46 cases of atrophy in 189 patients with Addison's disease. In the individual series noted, the incidence of atrophy ranged from 10 to 50 per cent. Anderson's recent case report was offered as being one of adrenal atrophy. In our own patient, a hemorrhagic diathesis at the age of 2 may well have resulted in adrenal involvement with subsequent fibrosis and atrophy, while the severe illnesses of later life may, in themselves, have initiated such a process or contributed to the already present degeneration. It is of interest that dietary inclinations toward salty food manifested themselves early in life. These may well have been concomitant with early adrenal involvement. Richter (9) has shown that there is a prompt sodium chloride craving in his adrenalectomized rats which is alleviated by administration of desoxycorticosterone.

The etiology of the meningeal irritation and spinal fluid changes remains obscure. Although at first it was felt that the probable explanation was tuberculous meningitis, the child's course and the subsequent laboratory findings did not substantiate such a premise. It is felt, in retrospect, that this acute meningeal episode bore no immediate relationship to the primary adrenal deficiency in the patient, and that a lack of adrenal cortical hormone probably did not produce the meningeal symptoms.

#### SUMMARY

A 7-year-old white boy with pigmentation, clinical findings and crises resembling those of Addison's disease is presented. An attempt to perform the Cutler-Power-Wilder excretion test resulted in severe crisis before the test could be completed. Clinical response to adreno-

cortical hormone and salt was prompt and adequate. The etiology remains obscure. It is hypothesized that adrenal damage occurring early in life from severe illness resulted in atrophy of these glands. However, tuberculous involvement has not definitely been disproven.

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# Value of Desoxycorticosterone Acetate in the Treatment of Peripheral Vascular Diseases

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IN THE TREATMENT of thrombo-angiitis obliterans and of arteriosclerosis obliterans all will agree that successful therapy would encompass arrest of the disorder, maintenance of the circulation, and, if possible, increased circulation through the development of collateral vessels. Among the many methods and modalities of treatment advocated to achieve these results is the intravenous injection of a hypertonic solution of sodium chloride. A 2 to 5 per cent solution is injected 3 times weekly in amounts of 300 cc. or less, over long periods of time. Promotion of collateral circulation is the special forte of this treatment, which increases the volume and lessens the viscosity of the blood, effects which may be enhanced by the osmotic action of the sodium chloride itself.

Although no specific effect of this salt in thrombo-angiitis obliterans or in arteriosclerotic obliterans is claimed and although no deficiency in its ions has been shown to exist in these disorders, the remarkable benefits of salt therapy in many cases cannot be gainsaid. That salt metabolism is in some way intimately involved is apparent, and immediately invites speculation as to the possible rôle of the adrenal cortex which is concerned in regulating electrolyte metabolism. This gland becomes increasingly suspect when it is realized that the effect of its cortical hormone is to increase blood volume and lower blood viscosity. It is reasoned that a greater secretion of adrenal cortical hormone should increase the blood sodium chloride, increase blood volume, and lower blood viscosity and therefore should, within limits, have the same effect in thrombo-angiitis obliterans and arteriosclerosis obliterans as does intravenous hypertonic sodium chloride solution. It follows that the beneficial effects of sodium chloride solution, which benefits, theoretically, could be produced also by

increased adrenal cortical activity may actually indicate an existing hypo-adrenia.

A comparison of the symptom complex of functional hypo-adrenia with the clinical picture presented in cases of thrombo-angiitis obliterans and arteriosclerosis obliterans, brings out a striking similarity. In common are the asthenia, muscle fatigue, sensitivity to cold, cold extremities, low rate of metabolism and hypotension. That, in these cases, a state of hypo-adrenia may exist suggests itself more and more, therefore, and would serve to explain further the beneficial effects of the salt solution. If deficient cortical activity does exist, then the hormone synthesized by Steiger and Reichstein, besides influencing the distribution of electrolytes and fluids, may also exert a specific effect. With this in mind, experimental use of desoxycorticosterone acetate in cases of thrombo-angiitis obliterans and arteriosclerosis obliterans seemed worthy of trial and an account of its use in 20 such cases is herein recorded.

## MATERIAL AND METHODS

The method followed was to prescribe desoxycorticosterone acetate in various unselected cases of thrombo-angiitis obliterans and of arteriosclerosis obliterans. With some patients the injection of the substance was the only form of treatment; the patients were allowed to continue smoking. The majority were patients who had had various forms of treatment previously, including intravenous saline, and it was felt that improvement, if any, specifically due to desoxycorticosterone acetate could be judged on a comparative basis. Subjective improvement was chiefly gauged by recording the number of blocks the patients could walk without pain, both before and after therapy. Clinical improvement was measured mainly by oscillometric and skin-temperature readings. The Pachon Boulitte oscillometer was used; a

McKesson Dermalor was employed in recording temperatures. Although room temperatures were not ideal, nevertheless by having each patient expose the feet for some time before the initial reading, with the room temperature approximately constant, any great discrepancy was overcome. The readings were spaced so that there was one-half hour of rest before the first reading, followed immediately by the injection; one-half hour later the second reading was taken. Even though no exhaustive study of method or procedure was attempted, a careful reading of the case reports will show that the treatment was given a fair trial and that *the study was controlled as carefully as possible.*

#### CASE REPORTS

*Case 1. W. B., male; age, 41 years, a Gentile of German descent. The onset of symptoms occurred 17 years ago with coldness of both hands and feet, intermittent claudication and a history of migrating phlebitis. The left leg was amputated below the knee 14 years before. The right foot showed trophic changes with a scarred, bulbous right big toe and absence of lanugo. No pulse was palpable around the ankle and there was marked plantar ischemia. Oscillometric readings ranged from zero to a faint trace. The blood pressure was 140 mm. Hg systolic, 90 diastolic; the urine was sugar free. The blood Wassermann reaction was negative, the blood count within normal limits, blood chlorides 560 mg. per 100 cc. and roentgen-ray study of the legs showed no calcification of vessels.*

The patient has been treated with saline 2 to 5 per cent and 300 cc., from once to 3 times weekly at various times for the past 10 years. Oscillometric readings showed that the main arterial tree was actually occluding in the right leg, but that a sufficient collateral circulation had developed for maintenance.

He was given desoxycorticosterone acetate, 10 mg. intramuscularly weekly, for a period of 6 months. He could walk 2 to 3 blocks without pain, initially, and this ability was maintained, although not improved upon. A drop in blood pressure was noted within  $\frac{1}{2}$  hour after a desoxycorticosterone acetate injection. Oscillometric readings showed an increase,  $\frac{1}{2}$  hour later, from a faint trace to a full 0.5. The patient's condition was maintained subjectively throughout this period with slight clinical improvement.

*Case 2. A. B., male; age, 40 years. Diagnosis, arteriosclerosis obliterans. The intermittent claudication had been worse in the calf of the right leg for the past two months. He could walk about a mile without pain. He smoked occasionally. The feet did not feel cold. All vessels, except the left dorsalis pedis, were palpable around the ankles. There was bilateral plantar ischemia; the oscillometric readings of the left ankle were 4.5 and of the right ankle, 5.5. The blood Wassermann reaction was negative and the urine clear. Roentgen-*

#### Case 2. READINGS DURING PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr. after
Blood pressure, mm. Hg	150/80	130/65
Skin temperature, °C., rt. toe/left toe	25.5/24.5	32.0/32.5
Oscillometric readings, rt. ankle/left ankle	7.0/8.5	8.0/8.5

ray examination of the legs showed calcification of the blood vessels.

The patient was given desoxycorticosterone acetate, 10 mg. intramuscularly, twice weekly. He repeatedly asserted that he felt much better after receiving the medication. He was able to walk as far as 2 miles at times without pain. He continued to smoke. The pulse of the left dorsalis pedis became palpable and oscillometric readings showed an increase. Of particular note in this case, in which readings were made  $\frac{1}{2}$  hour after an injection of desoxycorticosterone acetate, were: a) a fall in blood pressure, b) a rise in temperature readings of the skin of the feet, c) no change or slight improvement in oscillometric readings.

After 6 months of therapy the patient could walk indefinitely without pain. The oscillometric readings were maintained at a high level: right ankle, 8.0/left ankle, 8.0. The blood pressure reading showed a drop  $\frac{1}{2}$  hour after desoxycorticosterone acetate injections. The patient was grateful for what was being done for him. An increased collateral circulation need not have been achieved, but arterial spasm was overcome.

*Case 3. E. H., male; age, 60 years. Diagnosis, arteriosclerosis obliterans. He complained for the past year of pain in the calf of the right leg after walking  $\frac{1}{2}$  to 2 blocks. He was not diabetic and smoked a pipe. On examination both feet were found to be cold. There were no palpable pulses around the ankles and there was plantar ischemia of the right foot on elevation. Oscillometric readings were: right ankle, very faint; left ankle, 2.0; roentgen-ray examination of the legs showed early sclerosis in both lower extremities. The blood Wassermann reaction was negative and blood chlorides were 456 mg. The skin temperature reading were: right toe, 19° C./left toe, 20° C.*

The patient was given desoxycorticosterone acetate, 10 mg. twice weekly, as the sole form of treatment. Smoking was continued. The latter part of January, after 4 months of treatment, he said he felt much better and that he could walk a distance of 7 to 8 blocks without pain. The skin temperature readings were 24° C. in each foot. Recently he could walk as far as 10 blocks without pain; the pain when it came was not severe.

#### Case 3. READINGS DURING PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr. after
Blood pressure, mm. Hg	185/105	150/90
Skin temperature, °C., rt. toe/left toe	26.5/25.0	25.2/26.5
Oscillometric readings, rt. ankle/left ankle	1.5/3.0	1.5-2.0/3.0

*Case 4 A U*, female, age, 67 years The patient had been a known diabetic for the past 2 years For the preceding 4 weeks she had had pain in the left lower extremity when she walked as far as 1 to 2 blocks, and at night when in bed The left foot was colder than the right There was left plantar ischemia on elevation and the posterior tibial arteries were not palpable Oscillometric readings were right ankle, 0.5/left ankle, 0.5 skin temperature, right toe, 25° C /left toe, 25° C The urine contained sugar (she attends the diabetic clinic) The blood Wassermann reaction was negative and skiagrams of the legs showed calcification of the vessels in both extremities

Treatment with desoxycorticosterone acetate, 10 mg weekly, produced no improvement She is highly sensitive and emotional and this therapy was discontinued sooner than had been anticipated

*Case 5 H J*, male, age, 43 years Diagnosis, arteriosclerosis obliterans There was an onset of pain in the sole of the left foot, and intermittent claudication developed 4 months ago The patient could walk a distance of 4 blocks without pain

The general condition was good, the left foot colder than the right There was left plantar ischemia The pulse around the ankles was palpable with the exception of that of the left dorsalis pedis Oscillometric readings were, right ankle, 3.5/left ankle, 0.25, skin temperature readings, right toe, 33° C /left toe, 32° C The urine was clear, the Wassermann reaction negative the blood chlorides were 475 mg Skiagrams of the legs showed arteriosclerotic changes in the vessels The blood pressure was 130 mm Hg systolic, 80 diastolic

The patient was given adrenal cortical extract 2 cc intramuscularly twice weekly There was subjective improvement, and he could walk as far as 10 blocks without pain However, there was no clinical improvement Oscillometric and temperature readings showed a decrease rather than an increase from the original readings

*Case 6 M S*, male, age, 41 years Diagnosis, thromboangitis obliterans The patient gave a history of painful feet for the past 4 years for which he had been treated as due to flat feet For the past 6 months his condition had become much worse There was no familial history of thromboangitis obliterans or of migrating phlebitis The hands were not affected He smoked 20 cigarettes daily

On examination rubor in the left foot and atrophy of the left leg were noted The right foot was pale No pulse was palpable around either ankle and there was bilateral plantar ischemia on elevation Oscillometric readings were, right ankle, 0.0/left ankle, 0.0, skin temperature readings, right toe, 28° C /left toe, 29° C The urine was clear, the Wassermann reaction negative Skiagrams of the legs showed no evidence of sclerosis The blood count was within normal limits The electrocardiogram showed no evidence of cardiopathy, the blood pressure was 120 mm Hg systolic, 80 diastolic There was discoloration of the gum margins

as in Addison's disease, however, there was neither asthenia, nausea nor vomiting

The patient was first given desoxycorticosterone acetate, receiving 10 mg intramuscularly twice weekly, he was instructed to take a teaspoonful of salt daily This form of treatment was continued from Oct 24, 1940 to Jan 23, 1941 He showed no improvement whatsoever and as the case was far advanced, saline therapy was instituted It is of interest to note that there has been no improvement with saline therapy up to this time A return to treatment with desoxycorticosterone acetate produced subjective improvement The clinical status, however, remained unchanged

*Case 7 J R*, male, age, 50 years Diagnosis, arteriosclerosis obliterans The onset of symptoms was 1 year ago with intermittent claudication of the calf

Case 7 READINGS DURING PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr after
Blood pressure, mm Hg	204/110	160/90
Skin temperature, °C		
rt toe/left toe	25/23	25.5/26.5
Oscillometric readings		
rt ankle/left ankle	0.0/3.0	0.0/4.0
Readings after cessation of therapy		
Blood pressure, mm Hg	175/110	150/90
Skin temperature, °C		
rt toe/left toe	28/29.4	28.4/30.8
Oscillometric readings		
rt ankle/left ankle	0.0/5.5	0.0/5.5

of the right leg only, the patient could walk a distance of but 1 block without pain He smoked 20 cigarettes daily Both feet were cold No pulse was palpable around the ankles and he had right plantar ischemia Oscillometric readings were, right ankle, 0.0/left ankle, 2.5, skin temperature readings, right toe, 19° C /left toe, 21° C Skiagrams of the legs showed early sclerosis of the vessels The urine was clear, the Wassermann reaction negative and the blood chlorides 350 mg per cent Desoxycorticosterone acetate injected twice weekly intramuscularly for 6 months resulted in marked subjective and clinical improvement The patient can walk about 10 blocks without pain and continues to smoke 10 cigarettes daily Oscillometric and skin temperature readings improved and it is interesting to note that the blood pressure continued to fall, contrary to the general belief that the adrenal cortical hormone produces a rise in blood pressure in all cases

*Case 8 J D*, male, age, 47 years Diagnosis, arteriosclerosis obliterans The patient reported pain in both heels for the preceding 6 months after walking a distance of 2 to 3 blocks He smoked 4 cigars daily There was no history of migrating phlebitis On examination all arteries around the ankle were palpable There was bilateral coldness of the feet and bilateral plantar ischemia Oscillometric readings were right ankle 2.5/left ankle, 2.0 The urine was sugar free, the Wassermann reaction negative, the electrocardiogram, normal

The patient was given 300 cc. of 3 per cent saline intravenously weekly from May 16, 1940 to Oct. 24, 1940, told to stop smoking and to take sitz baths following Buerger's exercises nightly. On this regime he did well. The symptoms markedly improved. He could walk as far as 2 miles without pain. The skin temperature readings were, right toe, 28° C./left toe 27° C. The blood pressure was 110 mm. Hg systolic, 70 diastolic.

From Oct. 24, 1940 to Jan. 23, 1941 he was given desoxycorticosterone acetate, 10 mg., intramuscularly weekly with 60 grains of sodium chloride daily by mouth. He claimed that the improvement had been maintained. He could still walk 2 miles without pain. After a further period of 4 months of this therapy he could walk without pain and considered himself very much improved. After therapy with desoxycorticosterone acetate the blood pressure was 110 mm. Hg systolic, 70 diastolic; the skin temperature readings were, right toe 27.4° C./left toe, 27.0° C. The oscillometric readings were, right ankle, 4.0/left ankle, 4.0.

*Case 9. J. D., male; age, 43 years. Diagnosis, arteriosclerosis obliterans. The onset of symptoms had occurred 5 years ago with pain, chiefly of the left foot and ankle. He could walk a distance of but 1 block without pain. There was no history of migrating phlebitis nor a familial history of thrombo-angiitis obliterans. He smoked 3 packs of cigarettes per week.*

On examination the left foot was found to be colder than the right. The right anterior tibial artery was palpable but no other vessels around the ankles were left. There was left plantar ischemia and the oscillometric readings were, right ankle, 2.0/left ankle, 0.75. The skin temperature readings were, right toe, 25° C./left toe, 25.5° C.

The urine was clear and the blood Wassermann reaction negative. A skiagram of the legs showed early calcification of vessels. He was given desoxycorticosterone acetate, 5 mg. weekly; later this was increased to 10 mg. twice weekly. In 2 months he could walk about one mile without pain. After 6 months he was able to walk several miles without pain and said he was a 'new man.' The oscillometric readings increased slightly in the right ankle but decreased in the left. Six months after the institution of treatment the readings were: blood pressure, 130 mm. Hg systolic, 80 diastolic; skin temperature, right toe, 29° C./left toe 29.5° C.; oscillometer, right ankle, 3.0/left ankle, 0.5.

*Case 10. M. S., male. Symptoms and signs of arteriosclerosis were present. He complained of heaviness and weakness of both thighs, pain in both legs and feet, and general fatigue. Salicylates and tonics which had been given him in another clinic had not helped the condition. Examination of the legs revealed no trophic changes. The right foot was colder than the left; all pulses around the ankles were palpable, but there was slight left plantar ischemia. Oscillometric readings were, right ankle 0.5/left ankle, 0.5; temperature readings, right toe, 31° C./left toe, 32° C.*

The urine was free of albumen and sugar; the blood

Wassermann reaction was negative; an electrocardiogram revealed a normal cardiac status with a blood pressure of 135 mm. Hg systolic, 70 diastolic. A skiagram of the legs showed early sclerosis of the blood vessels. He was given 2 per cent saline intravenously, 3 cc., sitz baths and Buerger's exercises daily and not allowed to smoke. This treatment was maintained for many months with only slight improvement. Desoxycorticosterone acetate, 10 mg. intramuscularly was instituted in place of the saline. The patient improved generally, the fatigue lessened and he walked better without pain and for longer distances. The blood pressure did not vary, the skin temperature readings remained about the same, but, contrary to most cases the oscillometric readings increased from time to time without maintaining the upper levels, showing that spasm of the vessels had been temporarily relieved.

*Case 11. B. M., male; age, 56 years. Diagnosis, arteriosclerosis obliterans. There was pain in the left thigh and calf on taking 5 steps; the onset occurred about 3 years ago. He smoked 10 cigarettes daily. On examination the feet felt cold and no pulse around the ankles was palpable. He had marked left plantar ischemia on elevation (Samuels' test) and oscillometric readings of right ankle 1.5/left ankle 0.0; skin temperature readings, right toe 20° C./left toe 20° C.*

The urine gave a slight trace of albumen but no sugar. The blood Wassermann reaction was negative; the blood chlorides 410 mg. per 100 cc. and blood cholesterol 180 mg. Roentgen-ray examination showed moderate sclerosis of the arteries of both legs. The patient was told he could continue smoking and receive 10 mg. of desoxycorticosterone acetate twice weekly while taking a teaspoonful of salt daily. After 7 months of therapy there was no marked subjective improvement. Clinically there was some evidence of improvement. The blood pressure was 140 mm. Hg systolic, 75 diastolic; oscillometric readings, right ankle, 1.5/left ankle, 0.0; skin temperature readings, right toe, 27.8° C./left toe 29.0° C. The increase in temperature readings would seem to indicate peripheral vasodilatation.

*Case 12. J. K., male; age, 47 years; Jewish male of Polish extraction. Diagnosis, thrombo-angiitis obliterans. The onset of symptoms occurred in 1935 when, due to massive gangrene of the left foot, that leg was amputated. Since then there has been claudication pain in the calf of the right leg enabling him to walk only 1 to 2 blocks without stopping. The right foot was cold but showed no trophic changes. No pulse could be felt around the ankle and there was marked plantar ischemia on elevation. Oscillometric readings around the right ankle have varied from zero to 1.0 in the past few years. The roentgen-ray findings were negative; the urine was clear; the blood Wassermann reaction negative; the blood study showed 103 per cent hemoglobin, red blood cells 4,850,000, white blood cells 7,800; the differential count was normal.*

He has remained under treatment for several years since the amputation, receiving the usual advice to

## Case 13 READINGS DURING PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0 5 hr after	Before therapy	0 5 hr after	Before therapy	0 5 hr after
Blood pressure, mm Hg	116/70	110/70	105/70	105/65	105/60	105/70
Skin temperature °C, rt toe/left toe			21 0/25 5	23 8/22 2	30 5/33 0	31/33 5
Oscillometric readings rt ankle/left ankle	6 0/7 0	7 0/7 0			6 0/8 5	6 0/9 0

## Case 14 READINGS DURING COURSE OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0 5 hr after	Before therapy	0 5 hr after
Blood pressure, mm Hg	120/75	110/70	105/70	105/75
Skin temperature °C, rt toe/left toe	22 5/21 8	24 8/24 8	21/21	21 8/21 2
Oscillometric readings rt ankle/left ankle	0 0/0 0	0 0/0 0	0 0/0 0	0 0/0 0

refrain from smoking, he has taken Buerger's exercise and sitz baths, and in addition, intravenous saline, 300 cc varying from 2 to 5 per cent. He was also given tissue extract for a period of time but felt better when taking the saline. He had poor arm veins so that the external jugular veins were being used for the injections—not without some misgiving. He was given desoxycorticosterone acetate, 15 mg intramuscularly 3 times weekly for several months. Skin temperature readings were not recorded but blood pressure and oscillometric readings were made frequently before and ½ hour after the desoxycorticosterone acetate injections. Following most of the injections there was a drop in blood pressure of 10 to 20 points. There was never a rise in blood pressure. Oscillometric readings showed no increase after the injections and ranged between 0.5 and 1.0 at the right ankle. Some days he felt better than other days and reported he could walk as much as 3 blocks without having to stop. He experienced thirst and a salty taste in his mouth after the injections, similar to that following saline therapy. No definite improvement was obvious but the patient maintained that he felt better at times, although not consistently so. The desoxycorticosterone acetate injections may have maintained his system in the same state as did the saline injections, but it is possible that some of his sense of well being was psychological.

Case 13 J H, age, 30 years, male, Gentile with a history and symptoms suggestive of thromboangiitis obliterans. The onset of symptoms occurred 8 years ago but the right foot has become really troublesome only recently. A history of migrating phlebitis was obtained. He could not walk more than 10 to 15 blocks without pain. He was a pipe smoker. On examination the feet had a good color, there were no trophic changes, the right foot felt colder than the left, and pulsations of the dorsalis pedis, anterior tibial and posterior tibial arteries, although felt in the left foot, could not be palpated in the right foot. Plantar ischemia on elevation could be discerned on the right foot. Oscillometric readings were, right ankle, 5.5/left ankle, 8.0. The heart findings were normal, the urine clear, blood Wassermann reaction negative and roentgen ray study showed no calcification of blood vessels. Following therapy with intravenous saline he felt very much improved and could walk great distances. He was then given desoxycorticosterone acetate, 10 mg

intramuscularly twice weekly to see if this improvement could be maintained. During this trial period the condition did not regress but he was never quite as happy as when receiving saline therapy.

Case 14 M M, male, age, 47 years. Diagnosis, arteriosclerosis. For the past 4 years he has had pain in the buttocks with claudication pain in the calves of legs after walking one block. In the past 2 years the symptoms have become progressively worse. He claimed to have stopped smoking in recent years. On examination of the lower extremities, there were no trophic changes, both feet were cold, the right more so than the left, both anterior tibial arteries were faintly palpable but neither the posterior tibial nor dorsalis pedis pulse was felt. He had bilateral plantar ischemia and the oscillometric readings were zero at either ankle. The urine was sugar free but showed a slight trace of albumen, the blood Wassermann reaction was negative and roentgenograms of the legs revealed calcified plaques in the upper tibial arteries. Cardiac examination and electrocardiogram showed myocardial infarction with insufficiency and coronary closure.

He was given the usual instructions and received tissue extracts by intramuscular injections. Intravenous saline could not be used in this case because of the cardiac status. He obtained no relief with the tissue extracts so that desoxycorticosterone acetate, 10 mg intramuscularly twice weekly, was substituted. During an 8 months' trial varied results were obtained. Blood pressure, temperature, and oscillometric readings were made at intervals. At times he felt improved, on which occasions there was a drop in blood pressure with a rise in temperature following treatment with desoxycorticosterone acetate.

For a period of two months he was given a combination of 5 mg of desoxycorticosterone acetate and 0.5 cc of tissue extract, intramuscularly. During this period it seemed that general improvement had been greater with desoxycorticosterone acetate therapy alone. It is to be noted that for a patient with this degree of arteriosclerosis, the blood pressure can be considered low.

Case 15 I L, male, age, 55 years. Diagnosis, arteriosclerosis obliterans. He has had diabetes for the past 8 years and presented himself complaining of claudication pain in the calf of the right leg after walking a distance of 2 to 3 blocks. The onset of symptoms



### Case 15. READINGS DURING THE COURSE OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr. after	Before therapy	0.5 hr. after
Blood pressure, mm. Hg	154/80	154/80	150/85	155/85
Skin temperature, °C., rt. toe/left toe	33/33	33.2/33.2	32/32.8	32.6/33.4
Oscillometric readings, rt. ankle/left ankle	1.5/2.5	3.0/3.0	1.5/2.5	1.5/3.5

was 6 months earlier. He smoked between 1.5 and 2 packs of cigarettes per day. On physical examination, there were no trophic changes; the feet were of good color and the right dorsalis pedis and right and left anterior tibial arteries were palpable. Had had plantar ischemia in the right foot and the skin temperature readings in both the right and left toes were 33° C.

The oscillometric readings were, right ankle 1.5/left ankle 2.5. The urine analysis gave normal results, the blood Wassermann reaction was negative; roentgenograms of legs showed no calcification and electrocardiograms showed some myocardial damage. The blood chlorides were 538 mg.

The usual advice was given and treatment consisted of desoxycorticosterone acetate, 5 mg., 2 times weekly. Blood pressure, temperature readings and oscillometric readings were made from time to time both before and 0.5 hour after the desoxycorticosterone acetate injections. On only two occasions did a rise in blood pressure occur. At all other times there was a lowering or no change after the injections. The majority of the skin temperature readings showed a rise from .2 to 1.4° C. Oscillometric readings either remained the same or showed an increase.

Subjectively, he could walk longer distances without pain—as much as 5 or 6 blocks. However, he was never completely free from pain so that often he would come in saying he felt no better. In this case the readings showed clinical improvement when the patient complained he felt no better.

*Case 16. A. K., male; age, 50 years. Diagnosis, arteriosclerosis obliterans. He has had trouble with his feet for about a year and a half and could walk but 4 to 5 blocks without pain. He also complained of burning and tingling of the feet. He smoked 40 cigarettes daily. There were no tropic changes of the feet and no varicosities. The feet felt warm to the touch. He had bilateral plantar ischemia which was more marked on the left foot. No peripheral pulse was palpable. Oscillometric readings were, right ankle, 0.5/left ankle, 1.0. The results of urine analysis were normal and the blood Wassermann reaction was negative. Roentgen-ray examination of the legs showed calcification of the blood vessels.*

Besides the usual advice and home treatments he

#### Case 16. READINGS AT ONE TIME DURING COURSE OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr. after
Blood pressure, mm. Hg	125/70	130/90
Skin temperature, °C., rt. toe/left toe	29.4/29.4	31.5/31.4
Oscillometric readings, rt. ankle/left ankle	1.25/0.5	1.25/0.5

was given intravenous saline for several months, with no improvement resulting either clinically or subjectively. He was then given desoxycorticosterone acetate and he said that he felt somewhat improved.

*Case 17. A. K., male; age, 58 years. He has had trouble with his feet for 12 years but first reported to the clinic 5 years ago. At that time he could walk a distance of 4 or 5 blocks without pain and there was no involvement of the upper extremities. After 3*

#### Case 17. READINGS AT ONE TIME DURING THE PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr. after
Blood pressure, mm. Hg	110/70	115/70
Skin temperature, °C., rt. toe/left toe	31.8/32.2	33.4/34.4
Oscillometric readings, rt. ankle/left ankle	0.0/0.5	0.0/0.5

months of treatment with diathermy and tissue extract he stopped attending the clinic, returning only when he could walk but one-half block without pain in the feet and calves of the legs. On physical examination there was no trophic changes; the pulse around the ankles was not felt and he had bilateral plantar ischemia. Oscillometric readings, right ankle, 0.0/left ankle, 1.0. The urine analysis gave negative results; the blood Wassermann reaction was negative and roentgen-ray examination showed no calcification of tibial vessels. An electrocardiogram revealed myocardial damage, probably with coronary involvement.

For 3 months he received mecholyl iontophoresis, diathermy and tissue extract but his condition progressively became worse. These treatments were stopped and he was given desoxycorticosterone acetate, 5 mg intramuscularly twice weekly. For 3 months these treatments also failed to give relief. He was then given both desoxycorticosterone acetate and tissue extract. During a two-month trial of this therapy he felt improved. He no longer has pain while resting; he can walk longer distances and the pain is not as severe as previously. There are no marked changes in blood pressure, skin temperature, and oscillometric readings. For his age and general condition, the blood pressure can be considered low. In this case, a drop in blood pressure following the desoxycorticosterone acetate injections was never observed.

*Case 18. H. S., male; age, 52 years. He originally complained of pain in the right foot and calf 8.5 years ago. He smoked about 20 cigarettes a day and gave no history of migrating phlebitis. A diagnosis of thromboangiitis obliterans was made at that time and he improved with saline therapy. He stopped treatment for about 8 years and recommenced smoking. He felt*

well until recently when he complained of pain in the left foot and calf on walking. On examination the feet were of good color with no trophic changes or ulceration. The right dorsalis pedis artery was palpable but no other pulse around the ankles was felt. He had marked bilateral plantar ischemia. The skin temperature readings were, right toe, 27.2° C /left toe, 26.4° C. The oscillometric readings were, right ankle, 5.0 /left ankle, 0.5. The urine was normal and the blood Wassermann reaction was negative. Roentgenograms showed no calcification of vessels.

*Case 15* READINGS AT ONE TIME DURING THE PERIOD OF TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	Before therapy	0.5 hr after
Blood pressure mm Hg	150/70	145/70
Skin temperature, °C, rt toe/left toe	30.2/30.6	33.2/31.0
Oscillometric readings, rt ankle/left ankle	5.0/0.5	4.5/0.5

He was given saline therapy but could walk a distance of only one block without pain. Therapy with desoxycorticosterone acetate, 5 mg intramuscularly, three times weekly was then instituted. During this period he felt better. He could walk a distance of 3 to 5 blocks without pain.

There were no marked clinical changes, although the temperature readings steadily improved and remained at higher levels. The blood pressure varied and was as low as 120/75 mm Hg.

*Case 19* J. G., male, age, 65 years. Diagnosis, arteriosclerosis obliterans. For the past 4 months he has had pain in both feet and could walk only one half block. The pain in the right foot was more severe than in the left. He smoked about 20 cigarettes daily. On physical examination, varicosities in both legs were found, but there were no trophic changes. The pulse of the left dorsalis pedis artery was palpable. The right foot was colder than the left with marked bilateral dorsal and plantar ischemia. The oscillometric readings were, right ankle, 0.0 /left ankle, 1.0. The skin temperature readings were, right toe, 30.6° C /left toe, 32.8° C. The urine was normal as was the blood Wassermann reaction. Roentgenograms revealed no appreciable vascular calcification in either leg.

The patient was allowed to continue smoking while receiving desoxycorticosterone acetate injections, 5 mg intramuscularly twice weekly. After a two month trial he reported no subjective improvement, although he felt that his condition was getting no worse. The oscillometric readings at this time showed some increase, right ankle, 0.0 /left ankle, 1.5.

He was then given tissue extract. The condition is becoming progressively worse. He has to stop several times while walking one block.

*Case 20* M. S., male, age, 62 years. Diagnosis, arteriosclerosis obliterans. He complained of pain and

coldness of the left foot for the past 5 months. The pain in the left foot came on after walking about 5 blocks. He smoked 7 or 8 cigarettes daily. He had no varicosities or trophic changes. The feet were cold, both left and right. No pulse was palpable around the ankles and there was left plantar ischemia. The oscillometric readings were, right ankle, 6.0 /left ankle, 0.0. There was a faint trace of albumen in the urine. The blood Wassermann reaction was negative. Roentgenograms of the legs showed no calcification and an electrocardiogram revealed no pathology. The blood pressure was 175 mm Hg systolic, 80 diastolic.

Therapy with desoxycorticosterone acetate 10 mg intramuscularly for 3 months, produced no improvement in the symptoms. There developed, however, a positive oscillometric reading, right ankle, 6.0 /left ankle, 1.0.

### CONCLUSIONS

1 The beneficial physiologic effect of hypertonic solutions of sodium chloride intravenously in thrombo angustis obliterans and arteriosclerosis obliterans can, within limits, be attained by intramuscular injections of desoxycorticosterone acetate.

2 The desoxycorticosterone acetate often appears to lower blood pressure, more often it may cause an increase in local skin temperature and occasionally an increase in oscillometric readings. A permanent lowering in blood pressure was not obtained. There is no doubt that rest was a contributing factor in those cases in which the blood pressure was lowered.

3 Because results in 20 cases of peripheral vascular disorders have been encouraging more extensive clinical trials of desoxycorticosterone acetate should be undertaken.

4 Desoxycorticosterone acetate cannot be regarded as a substitute for intravenous saline therapy, but it may serve as an excellent adjuvant for those clinicians who favor this form of treatment. It is useful in those cases in which intravenous technic or sudden increases in blood volume are contraindicated.

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The case reports were obtained from Peripheral Arterial Disease Clinics, Fourth Division, Bellevue Hospital, New York City, and Stuyvesant Polyclinic, New York City, Dr. Saul S. Samuels, Chief.

# Nutritional Therapy of Infertility in the Male, with Special Reference to the Vitamin B Complex and Vitamin E<sup>1</sup>

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IT HAS long been known that there is a relation between nutrition and fertility. Degenerative effects on the reproductive organs were among the most striking changes noted in early work on deficiencies of vitamin A, the vitamin B complex and vitamin E (1, 2, 3). Among these, the B vitamins have received less attention in this respect than the other two. Changes in the reproductive system in vitamin B deficiency have been variously attributed to an associated vitamin E deficiency and to the inanition which occurs in depletion of the B vitamins.

With the isolation, identification and synthesis of various factors of the B complex, re-investigation of the early work has already yielded further information. Lepkovsky and Krause (4) found in the study of pantothenic acid deficiency that if control animals were restricted in food intake so that their body weight approximated that of animals deficient in pantothenic acid, the percentage difference in the weight of the testes in the two groups exceeded several-fold that in body weight or food intake.

Among a group of male patients examined by us during the past year because of sterility, we were impressed by the presence, in several, of lesions indicative of more or less severe vitamin B deficiency such as glossitis, stomatitis and lesions of the skin. These men com-

plained of headaches, irritability, insomnia; mental depression, easy fatigability and lumbar backache. Although all but one appeared well-nourished, they gave histories of subsistence on grossly inadequate diets for many years.

We were led to attempt nutritional therapy in these patients not only because of the known relation of nutrition and fertility but also because of the experimental finding by one of us (M. S. B.) that the liver loses its ability to inactivate estrogen in deficiency of the vitamin B complex (5, 6, 7). In contrast, the inactivation of androgen in the liver was not significantly affected in B avitaminosis (8). The excess of free estrogen and the alteration in the estrogen-androgen equilibrium which thus result might be expected to affect adversely spermatogenesis as well as other functions of the endocrine system.

In male patients with cirrhosis of the liver, now known to result from nutritional deficiency, Glass, Edmondson and Soll (9) have shown that there is a considerable excess of estrogen in the urine and that all, or almost all of it appears in active, uncombined form; the amount of androgen in the urine was less than that of normal control males, and none of it appeared in free form. The patients studied by Glass and his associates had testicular atrophy; gynecomastia or both.

None of the patients included in the group to be reported here had gynecomastia, but two of them had definite testicular atrophy (excluding one case in which unilateral atrophy

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ollowed an operation for varicocele). The occurrence of testicular atrophy in nutritional deficiency was reported by Reynolds and Maomber (10) more than 20 years ago.

For the most part, nutritional therapy in our patients was concerned with the vitamin B complex. A few patients received added supplements of vitamins A, D and C. A few that did not respond to B complex alone received synthetic vitamin E in addition.<sup>2</sup>

When the diet was grossly inadequate, instructions were given as to its correction, requiring inclusion of whole grains, fresh vegetables, fruits, dairy products, liver and meat, with limitation of intake of refined carbohydrates. In contrast to ingestion of the vitamin supplements, which, being 'medicine' were taken religiously, the dietary instructions appear to have been observed rather casually.

In 6 patients, examinations of the spermatic fluid were made biweekly or at monthly intervals during treatment. In others, when this was not possible, a specimen was examined before treatment was instituted and, in 2 cases, again shortly before impregnation occurred; in another case the second examination was made at the same time as the Friedman test, which proved positive. In 3 other cases in which impregnation occurred, only the initial sperm counts are as yet available.

Following initial success in the treatment of patients with obvious signs of nutritional deficiency, this therapy was extended to others living on a so-called 'normal' diet, who showed no noteworthy objective signs of impaired nutrition. Response to therapy was even better than in the original group; it seems not improbable that these apparently normal individuals had a low-grade nutritional deficiency.

#### CASE REPORTS

*Case 1, (J. K.),* age 39, had a 13-year-old daughter by a previous marriage. He had been married to his second wife (age 29) about 8 months when he was first seen early in September, 1941. At that time he had a sperm count of 20,000,000 per cc.; total 44,000,000; motile forms, 50 per cent; abnormal forms, 45 per

cent. Previous examination of the wife revealed no abnormalities except for the possibility of a small fibroid in the right uterine cornu. The tubes, at first closed at a pressure of 200 mm. Hg, 10 weeks later were open at a pressure of 130 mm.

*J. K.,* when seen in October, 1941, appeared apprehensive and depressed; he gave a history of a severe emotional disturbance following the death of his first wife several years previously. Formerly abstemious, he began to drink, neglected his diet and lost considerable weight. Subsequent to his second marriage his consumption of alcohol became more moderate and he paid more attention to his diet, although this was still deficient, partly due to use of a bland diet prescribed several years previously for a 'chronic appendicitis'; he no longer complained of abdominal pain.

Examination revealed a somewhat undernourished man 69.25 inches in height, 147 pounds in weight. He had a lateral nystagmus which had been present for 15 years, bilateral astigmatism, not completely corrected; the conjunctivae were severely congested. There was a small area of dermatitis about the size of a dime on the left side of the upper lip. This had been present for 5 years and had resisted repeated therapy with local applications and roentgen irradiation. The tongue was markedly edematous and showed deep indentations from contact with the teeth, there were numerous deep, red fissures which were very sensitive, and the papillae elsewhere were moderately atrophic. The teeth were in very poor condition; many had been extracted. The patient had an upper plate but, owing to tenderness of the gums, he had been unable to wear it for the preceding two months. There were numerous small ulcers on the inside of the lower lip.

The prostate was somewhat boggy but not enlarged; the testicles were soft and definitely smaller than normal. The urine contained a large amount of ether-soluble red pigment but was otherwise normal.

The patient was advised to take 2 heaping teaspoonfuls of brewer's yeast 3 times a day with meals and was given, in addition, 20,000 units of vitamin A, 2000 units of vitamin D and 50 mg. of ascorbic acid per day. When seen 2 weeks later he had gained 4 lb.; he was unable to take a full dose of the yeast because of flatulence and had reduced it to from 1 to 2 teaspoonfuls a day. The source of B complex was changed to 6 capsules a day of a fortified B complex preparation derived from liver, providing 6 mg. of thiamin, about 3.6 mg. of riboflavin and 60 mg. of niacin per day. A specimen of urine examined 2 weeks later contained no ether-soluble red pigment.

The patient was seen 3 days later, after slightly more than a month of treatment. The lesion on the upper lip had healed completely for the first time since it had appeared 5 years previously; he was much less apprehensive, reported that he felt much better generally, was less troubled by eyestrain and could now wear his dental plate. The tongue was less sensitive but showed little objective improvement. The ulcers on the lower lip had healed.

<sup>2</sup> Care was taken that the vitamin E was administered between meals on an empty stomach, to avoid possible destruction of the  $\alpha$ -tocopherol through contact with rancid fat in the digestive tract; rancidity which might be developed in fats through processes ordinarily used in cooking is highly destructive to vitamin E.

Unfortunately it was not possible to check the sperm count of this patient subsequently. His wife was seen in April, 1942, at which time she was pregnant; her last period had occurred on February 1.

*Case 2, (N. W.),* age 27, had been married for 6 years. Precautions had been taken against pregnancy for the first 5 years of this time. Examination of his wife, age 26, showed no abnormalities.

A sperm count on *N. W.* in December, 1941, showed: 14,000,000 per cc.; total, 84,000,000; motile forms, 30 per cent; abnormal forms, 36 per cent. This patient had had severe acne on the face, chest and back since he was 15 years of age. He had received roentgen therapy to these regions with improvement in the acne; there were still a few pustules on the face, which was deeply scarred from the healed lesions. Three years previously he had been operated upon for a left varicocele. After the operation the left testicle atrophied. He had been sensitive to ragweed and had hay fever, not relieved by attempts at desensitization. Aside from the hay fever, he had frequent attacks of rhinitis throughout the year. His diet, while not adequate, did not appear to be seriously deficient.

Physical examination of *N. W.* revealed no abnormalities except for the acne, already mentioned, and a left testicle about  $2 \times 1 \times 0.5$  cm. The right testicle appeared normal. The urine contained a large amount of ether-soluble red pigment.

A fortified liquid preparation of vitamin B complex derived from liver was prescribed in a dose of 2 teaspoonfuls 3 times a day; this provided per day: thiamin 9 mg., riboflavin 3.6 to 4.8 mg., niacin amide 60 mg. This was later increased to 8 teaspoonfuls a day, and from 50 to 75 mg. niacin amide in addition. After 2 months of therapy the ether-soluble red pigment in the urine had diminished to a trace; the sperm count was 18,400,000 per cc.; total, 154,560,000; motile forms, 75 per cent; abnormal forms, 22 per cent. At this time *N. W.*'s wife was pregnant.

*Case 3, (J. S.),* age 31, when seen in February, 1942, had been married for more than 3 years. Precautions against pregnancy had been taken for the first 2 years of this time. His wife, age 28, showed no abnormalities except a slight enlargement of the right ovary; the fallopian tubes were patent at a pressure of 60 mm. Hg.

A sperm count on *J. S.* on Feb. 10, 1942, showed 190,000,000 per cc.; total, 490,000,000; abnormal forms, 23 per cent. Only 1 or 2 sperm were motile in each high power field. The past history was essentially irrelevant, except that the patient reported a noticeable increase in fatigability during the preceding 2 or 3 years, associated with lumbar backache and pain in the calves of the legs. On physical examination the only positive finding was a moderate but definite atrophy along the margins of the tongue. For 4 months *J. S.* received 6 capsules a day of a fortified vitamin B complex preparation derived from liver, together with supplements of 150 mg. of niacin amide, 20,000 units of vitamin A, 2000 units of vitamin D and 50 mg. of

ascorbic acid. At the end of this time the sperm count was 178,000,000 per cc.; total, 645,000,000; abnormal forms, 14 per cent. But still only 5 per cent were motile. The patient reported that he felt much stronger physically and was of a more cheerful disposition. He had recently played tennis for 2 hours at a stretch without undue fatigue; he no longer had backache or pain in the legs. The glossitis had improved.

Because of the continued necrostermia,  $\alpha$ -tocopherol acetate was given in 3-mg. doses 3 times a day, on arising, and from 1 to 2 hours before meals.<sup>2</sup> After 6 weeks, the seminal fluid, while unchanged in other respects, had 41 per cent of actively motile forms. Five weeks later this had risen to 68 per cent. At this time the number of abnormal forms had diminished to 12 per cent. The progressive increase in motility in this case was very striking.

*Case 4, (W. L.),* age 28, had been married for 4 years. No precautions had been taken against pregnancy. His wife, age 23, showed no pelvic abnormalities; the fallopian tubes were patent.

On Oct. 28, 1941, a sperm count on *W. L.* showed only 2,100,000 in the whole specimen (0.9 cc.); 70 per cent were motile, 35 per cent abnormal. This patient gave a history of a seriously deficient diet; the only vegetable he ate was potato, the only fruit, a small amount of orange juice. He had otherwise subsisted for years on meat, eggs and pastries. He complained of severe migrainous headaches which were invariable on Sundays and holidays when he disturbed his usual routine. He had continuous lumbar backache, he was easily fatigued. During the prededing few months he had noticed a definite diminution in libido.

Physical examination revealed a moderate edema of the tongue, which showed deep indentations at areas of contact with the teeth, but there was no actual glossitis. The gums were soft, spongy, and bled easily; the teeth were in poor condition. Both testicles were soft and definitely atrophic.

For a period of 7 months this patient received 6 teaspoonfuls per day of a vitamin B complex preparation derived from liver, with supplements of niacin amide, 50 to 150 mg. per day, and vitamins A, D and C as indicated in *case 3*. Within a month the headaches and lumbar pain disappeared and have not recurred. There was marked improvement in general health and well-being and increased libido. However, repeated examinations of the spermatic fluid showed only moderate improvement. On June 8, 1942, the count was 9,200,000 per cc.; total, 44,160,000; 64 per cent motile; 31 per cent abnormal.

Alpha-tocopherol acetate was then given as in *case 3*. In 6 weeks the count was 31,500,000 per cc.; total, 94,500,000, motile forms, 90 per cent; abnormal forms, 25 per cent. Two months later, the count was 41,700,000 per cc.; total, 200,160,000—a several-fold increase.

In 5 other cases impregnation occurred after variable periods of therapy with vitamin B

complex alone.<sup>3</sup> In 2, only the initial sperm count is as yet available. In the other 3, in which the second count was made shortly before or shortly after impregnation, there was no significant change in the number, physical character or motility of the sperm. In one of the latter cases abortion occurred at about the fourth month of pregnancy.

In another case, for an account of which we are indebted to Dr. Edward A. Horowitz, sterility had persisted for 15 years. This patient, at our suggestion, received vitamin B complex and vitamin E and was instructed as to his diet. Within two months impregnation occurred.

Three further cases complete this series. In two of these, definite signs of nutritional deficiency were present. Under therapy with vitamin B complex alone both showed physical improvement together with an increase in the number of sperm and definite diminution in the percentage of abnormal forms. Impregnation had not occurred after 3.5 and 4.5 months of treatment, respectively, and both patients are now receiving  $\alpha$ -tocopherol acetate<sup>4</sup> in addition.

The third patient had almost complete azoospermia; after centrifugation only one or two sperm could be found during prolonged search in an occasional specimen, although the sperm that were found were extremely active. This patient had a history of diphtheria in childhood, followed by months of complete disability. Since a few sperm could be found it was thought worthwhile to try vitamin B complex therapy; after 4.5 months there was no detectable change in the spermatic fluid.

#### DISCUSSION

It has been shown by Hotchkiss (11) that fairly wide variations occur spontaneously in semen specimens obtained from the same subject at different times. It may well be questioned, therefore, whether the changes ob-

served by us may properly be ascribed to the treatment employed. In 5 of our cases, progressive improvement was noted in specimens examined at repeated intervals; it is unlikely that spontaneous variations would occur mainly in one direction and Hotchkiss (11) has further noted that men with relatively low sperm counts did not subsequently submit specimens that ranged into the higher levels and that the morphology in all specimens remained relatively constant. Among changes noted by us during therapy were, for example, an increase in the sperm count from 2,100,000 in the whole specimen to 41,700,000 per cc. and 200,160,000 in the whole specimen; a change in the percentage of motile forms from a small fraction of 1 per cent to 68 per cent; and diminution in the number of abnormal forms from 36 to 22, 23 to 12, 36 to 10 and from 38 to 28 per cent. Huffman (12) has noted an inverse proportion between the number of sperm per unit volume and the percentage of abnormal forms.

The observations of Hamblen (13) and of Hotchkiss (14) indicate that occasionally a man with a comparatively low sperm count and a high percentage of abnormal forms may be fertile. In one of our cases impregnation resulted when the count was 18,400,000 per cc. (total 154,560,000) and the percentage of abnormal forms was 22. In another, the count was only 10,100,000 per cc. (total 36,360,000) with 27 per cent abnormal forms (this is the case, already mentioned, in which an abortion subsequently occurred).

Conversely, it is well known that motile sperm of apparently normal morphology are not necessarily fertile. This is illustrated in 4 of our subjects in whom there were initially 72,000,000, 68,000,000, 170,000,000 and 144,000,00 sperm per cc., respectively, of which 70 to 90 per cent were motile. No significant morphologic or other visible changes occurred during therapy, yet fertility was apparently restored.

In general, in the patients in whom fertility was restored in this series, the percentage of abnormal forms fell within the ranges suggested by Moench (15) as indicating the likelihood of fertility. In only one patient did the percentage of abnormal forms exceed the

<sup>3</sup> Among the preparations of vitamin B complex that have been used in this study are Vitamin B complex, Lederle Laboratories, New York City, oral and parenteral, Blexon, International Vitamin Corporation, New York City, Natuplex and Vitamin B complex, E. R. Squibb & Sons, New Brunswick, N. J., Beminal, Ayerst, McKenna & Harrison, Ltd., Montreal, Que., and Rouses Point, N. Y. Beta plexin, Winthrop Chemical Co., New York City.

<sup>4</sup> The vitamin E preparation used in these cases was Ephynal Acetate, Hoffmann La Roche, Inc. Nutley, N. J.

figure associated by Moench with the usual presence of sterility (25 per cent). As already mentioned, the wife of this patient aborted.

Belding (16) believes that the total sperm count is a more accurate index of fertility than is the number of sperm per unit volume, since variable dilution of the sperm undoubtedly occurs. On this basis our results appear more striking than indicated in the case reports; the total counts usually increased by a greater percentage than the number of sperm per cc. In addition to the data already mentioned, in one case in which the count per cc. varied between 22,700,000 and 39,700,000 during treatment, the total count increased, with fluctuations from time to time, from 24,000,000 to 119,100,000 with a peak at 140,000,000.

One of our patients had previously been treated elsewhere with a variety of gonadotropic and androgenic preparations, without the slightest response. Subsequent vitamin therapy led to prompt and definite objective improvement in the number, motility and morphology of the sperm.

The observations we have made thus far indicate that deficient spermatogenesis may be related to faulty nutrition, perhaps far more often than hitherto suspected. A review of some of the nutritional deficiencies of the so-called 'normal' modern American diet has recently been published by the Council on Foods and Nutrition of the American Medical Association (17). Because the extent of nutritional deficiency in the United States is only beginning to be appreciated, the relationship of dietary inadequacy to endocrine dysfunction has received little attention. Only 8 years ago, Meaker (18) indicated that nutritional deficiency was of little significance for human sterility, 'except as regards the matter of insufficient protein.' And this belief was reiterated by Kreutzmann (19) two years ago. In the last few years, however, the publications of Sebrell, Spies, Sydenstricker, Jolliffe and others have emphasized the extent of nutritional deficiency, especially of the B vitamins, among all strata of the American population.

That the vitamins are not the only nutritional factors of possible clinical importance in spermatogenesis is indicated in a recent study by Holt and his collaborators (20) on the dele-

terious effects of deficiency of certain amino acids, especially arginine, on production of sperm in human subjects. In the treatment of these patients it is important to take into consideration the frequent occurrence of multiple nutritional deficiencies.

One of the problems raised in this study is the question of response to vitamin E. Deficiency in  $\alpha$ -tocopherol in rats leads to irreversible changes in the testicle. As Mason (1) has pointed out, 'Even when vitamin E therapy is instituted coincident with the earliest appearance of histologic injury, the degenerative process continues to completion in all, or in the majority, of the seminiferous tubules. . . .' It remains to be determined whether the responses we have observed when vitamin E was given together with the B complex, after failure of the B complex alone to influence the sperm count sufficiently, constitute a real effect of vitamin E or a coincidental delayed effect of the B complex. The latter, in view of the time relationships, seems unlikely. But, with the patients in whom a control period of treatment with B complex preceded administration of vitamin E, no impregnation has yet occurred, despite improved spermatogenesis.

The relation of nutritional deficiency to the occurrence of sterility in the female is a problem which also requires study. For the most part, the wives of the patients in the series reported here ate substantially the same diet as did their husbands, and, as a consequence, their fertility may well have been impaired even though objective signs of deficiency were seen in only one of these women. Because of larger stature and greater energy output, men generally develop signs of deficiency more quickly and are likely to be more severely affected, than are women on the same diet. In a number of cases now under treatment both husband and wife are receiving nutritional therapy.

#### SUMMARY

Nutritional therapy, especially with the vitamin B complex, alone or in combination with vitamin E, was followed by improvement in the number, motility and morphology of the sperm in previously infertile men. In other cases of sterility in which initial specimens of spermatic

fluid were apparently normal, therapy with vitamin B complex alone apparently restored fertility without producing significant detectable changes in the sperm. Excluding one case of virtual azoospermia, among 12 cases so treated 8 impregnations occurred. The wife of one patient aborted at about the fourth month, the remainder, at the time of writing, are approaching term or have been delivered of normal babies.

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# Serum Diastase and Its Relation to Estrogen Metabolism in Pregnancy and the Menstrual Cycle<sup>1</sup>

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THE DETERMINATION of diastatic activity in the blood and urine is performed extensively as a diagnostic aid in suspected disease of the pancreas, high values being characteristic of acute pancreatic edema. Although the externally secreting cells of the pancreas have been considered by some as the source of diastatic activity, the presence of this enzyme in the blood after pancreatectomy has not been satisfactorily explained. Low levels have been reported in diseases associated with liver damage (1-5), but no one has been able to isolate the enzyme from the liver cell. Somogyi (1), in a recent review, concludes that its source is, as yet, unknown. Most investigators agree that under normal conditions its level in the blood is fairly constant, being unaffected by age, sex or diet.

Cope, et al., (6-8), working chiefly with dogs, have concluded that the internal secretions of all glands which are intimately related to carbohydrate metabolism influence serum diastase. In the dog, for example, they demonstrated sustained increases following hypophysectomy and adrenalectomy, and found the level of this enzyme a more sensitive index of adrenal insufficiency than changes in the nitrogenous or electrolytic substances of the blood.

In this laboratory blood and urinary studies of women during pregnancy and menstrual cycles have been concerned almost exclusively with the metabolism of the placental and ovarian hormones (9-15). That an intimate interre-

lationship between the various endocrine systems exists is well recognized although not fully defined. With the hope of throwing further light on this problem, especially the interrelationship between metabolism of the female sex hormone and those glands of internal secretion more directly involved in carbohydrate metabolism, it was decided to study the diastatic activity of the blood during periods of pregnancy and the menstrual cycle in which characteristic changes in estrogen and progesterone metabolism have been established.

## METHODS

Diastatic activity was measured by the method of Scharles and Salter (16) as modified by Cope, et al. (17), for its determination in serum. By this method, glycogen loss is measured rather than the endproduct of glycogenolysis. Results, therefore, indicate the number of mg. of glycogen lost after a 3-hour period of digestion at 43° C. of 2 cc. of solution buffered at pH 7.0, containing 1 per cent of glycogen. All determinations were made in duplicate and are based on the activity of a 10 per cent serum concentration.

Glycogen was prepared from rabbit liver by the method of Sahyun and Alsberg (18).

## EXPERIMENTAL RESULTS

*Normal late pregnancy, labor and the puerperium.* Specimens of blood were obtained repeatedly from 5 pregnant women during the last trimester and the puerperium. In 3 cases blood was also taken during active labor. Three of the 5 had diabetes, in all of whom the disease was being controlled by insulin and diet

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and in whom, as in the other 2 cases, the pregnancy was proceeding normally. The results are presented in figure 1. In all 5 cases the concentration of blood diastase exhibited a tendency to increase from the 30th week on. In 2 of them a marked peak was reached at 38½ and at 39½ weeks, respectively. Unfortunately, no blood was obtained at this period from the 3 cases of diabetic pregnancies. In the 2 patients, one a diabetic, from whom blood was taken within 3 days of the onset of labor, a decrease in blood diastase was found and in the 3 cases from whom specimens were taken during labor an even more marked drop was apparent. With *E. H.*, 3 analyses were performed during labor. The result of the first, at the start of mild contractions, did not differ significantly from that of the last previous analysis at 38 weeks. It is possible that a higher value intervened. The result of the second, made after 24 hours of strong contractions, was the lowest observed in this individual. An increased concentration of the enzyme was found 20 hours later, at the time of delivery, following a very prolonged and arduous labor. In this individual the only postpartum value, 6 days after parturition, had not altered from that at delivery, indicating, perhaps, that the patient had not fully recovered from an unusually difficult labor. In the other 4 cases the postpartum values were lower than any observed prior to the onset of labor. The activity was still low 30 days post partum in the only case studied after involution of the uterus.

No estrogen studies were made on these particular patients but a composite curve of urinary estrogens in 15 normal late pregnancies (13) is included in figure 1. The total active estrogens represent the rate of excretion of estrogens as such. The additional estrogenic activity acquired by zinc hydrogenation (unaccounted for  $T_{20}$  activity) supplies a gauge of the rate of estrogen degradation in the body (19). It is seen that the curves for the diastatic activity of the blood roughly parallel those for the rate of estrogen excretion and are inversely proportional to the rate of estrogen destruction. Our studies have shown that progesterin inhibits destruction and facilitates the rate of metabolic conversion of the estrogens (9-15). It would appear, therefore, that the in-

creasing production and utilization of the placental steroids between the 30th and 38th weeks of pregnancy is associated with rising levels of serum diastase; whereas, progesterin withdrawal and the increased rate of estrogen destruction which precede and accompany labor are associated with a precipitous drop in diastatic activity, low levels being maintained

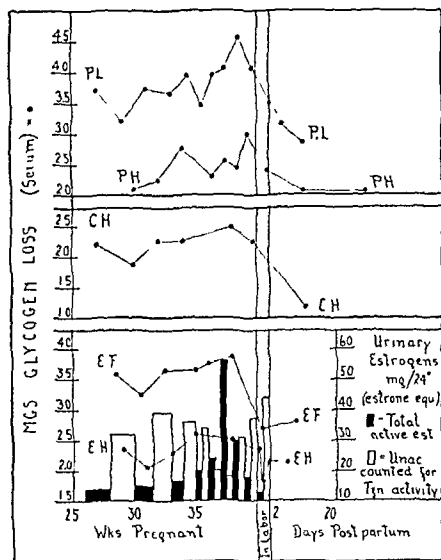


FIG 1 SERUM DIASTASE IN 5 NORMAL LATE PREGNANCIES AND URINARY ESTROGENS (COMPOSITE CURVES—15 CASES) *P L*, aged 20, para I, non-diabetic *P H*, aged 19, para I, non-diabetic *C H*, aged 25, para I, diabetes for 4 years, controlled by 80 to 100 units of protamine Zn insulin daily *E F*, aged 23, para I, diabetes discovered during second half of pregnancy, controlled by 80 to 100 units of protamine Zn insulin daily *E H*, aged 19, para I, non-diabetic, controlled by 80 to 100 units of protamine Zn insulin daily

for as long as one month post partum. In one case of prolonged labor a rise in serum diastase was observed following the initial drop.

The curves for blood diastase in pregnant diabetics (in whom the disease is controlled) do not differ from those of non-diabetic individuals. This same observation holds for the hormone balance (21). There is ample evidence that the diastatic activity of serum is altered in conditions of deranged carbohydrate metabolism such as prevail in cases of un-

controlled diabetes, in depancreatized animals (1, 2, 8, 20) or in normal animals in which hypoglycemia has been induced and maintained by insulin administration (8). The administration of insulin to depancreatized animals, however, restores normal levels of serum diastase. In diabetics, therefore, in whom the diabetes is controlled by insulin administration, as was the case in the 3 patients studied by us, no effect on diastatic activity

These contradictory results may be accountable in part to the diverse methods employed for serum diastase determination, and in part to the fact that most investigators have based their conclusions on composite findings rather than on successive specimens from the same individuals. Our repeated analyses indicate that although the diastatic activity of the blood from any given individual is fairly constant, there is a wide range over which the values may lie in different individuals. A total of 10 analyses were performed on other women during the last trimester of normal pregnancy. Including these with those presented in figure

TABLE 1. SUMMARY OF DATA ON SERUM DIASTASE IN WOMEN

	No. of Cases	No. of Bloods	Mg. Glycogen Loss <sup>1</sup>	
			Range	Average
Normal late pregnancy				
Before labor	11	44	0.95-4.59	2.85
During labor	3	5	1.85-2.40	2.65
After delivery	5	8	1.18-3.15	2.33
Late pregnancy complications				
Pre-eclampsia & eclampsia	9	26	1.02-4.37	2.21
Fetal death	2	12	1.35-2.36	1.82
Total diabetic pregnancies	7	48	1.02-3.84	2.23
Total non-diabetic pregnancies	15	50	0.95-4.59	2.58
Non-pregnant women throughout cycles	2	29	1.98-4.32	3.28

<sup>1</sup> From a 20-mg. solution of glycogen with a 10% dilution of serum.

would be expected. In the summary of our data on serum diastase (table 1) there is no significant difference between serum diastase in the diabetic and non-diabetic pregnancies and the parallel curves in diabetics and non-diabetics indicate that the changes observed in diabetic women during the course of normal late pregnancy, labor and the puerperium, and in late pregnancy complications, were typical of these conditions and in no way influenced by the diabetes itself or by the insulin administered.

The results reported in the literature on serum diastase during normal pregnancy are conflicting. Piano (22), in agreement with our data, finds a gradual rise in diastase up to parturition, with a drop to normal or below during the puerperium. Sugiyama (23, 24) and Goldschmidt-Fürstner (25), on the other hand, report lower values in pregnant than in non-pregnant women, with a rise to normal within 3 to 13 days post partum, while Spitzer (26) and Arneson and Morrin (27) detect no change in the diastatic activity of the blood associated with normal pregnancy or confinement. The latter, however, in agreement with our findings on *E. H.*, did note a rise during labor if the process was long and difficult.

1, the normal range of glycogen loss in late pregnancy from a 20-mg. glycogen solution, using 10 per cent serum dilution, lies between 0.95 and 4.59 mg. (table 1).

*Late pregnancy complications.* Three patients have been studied before and during the development of complications in late pregnancy. Previous publications from this laboratory have demonstrated that pre-eclamptic toxemia and eclampsia and certain cases of preterm delivery or stillbirth are preceded by an abnormal rise in serum chorionic gonadotropin (11, 14). This is accompanied by evidence from urinary analyses of a progressive deficiency of estrogen and progesterone culminating in the rapid destruction of estrogen which characterizes *a*) the onset of clinical signs in these diseases (14), *b*) the onset of normal labor (14) and *c*) normal menstruation (10, 15, 19). These hormone findings in all 3 of these patients showed the above abnormalities. Two of the patients developed pre-eclampsia about 6 weeks after the first rise in serum chorionic gonadotropin. The third, a patient with a history of stillbirth

was prophylactically treated with estrogen and progestin from the 31st week on, 6 weeks after the first rise in serum chorionic gonadotropin.

The serum diastase curves in these 3 cases are presented in figure 2. In each, the first abnormal increase in chorionic gonadotropin was followed by a steady drop in the diastatic activity of the serum. With two of them, *E. C.* and *F. M.*, this drop came before the 30th week and therefore cannot be considered abnormal when it is compared with the curves for normal pregnancy (fig. 1). With *S. L.*, however, the continued falling off in the level of serum diastase after the 30th week is the exact opposite of the normal findings. At 33 weeks albuminuria, the first clinical sign, was discovered. After 10 days of increasingly severe toxemia with hypertension and subjective symptoms, a transient rise in serum diastase was observed, while a blood taken the next day was again very low in diastatic activity. Labor was induced at 35½ weeks because of severe pre-eclampsia (a blood pressure of 180/110 mm. Hg., a trace of albumin and blurring of vision). A blood specimen taken at the start of mild contractions showed no change in diastatic activity. The baby died 24 hours post partum.

*E. C.* was the third<sup>2</sup> diabetic patient with toxemia in whom the hormone findings indicated an attempt at self-correction of the estrogen and progestin deficiency. The marked rise of serum diastase after the 30th week coincided with evidence from urine analyses of a corresponding rise in the production and conversion of the sex steroids. Aside from transient edema, this patient had been clinically well up to the 33rd week of pregnancy. At this time, facial edema was apparent and there was slight albuminuria (0.3 gm. per 24 hours). Toxic signs were never more than mild, the highest blood pressure reading being 135/88 mm. Hg. After 10 days of routine hospital care, the edema had disappeared but there was no decrease in albuminuria. At 34½ weeks spontaneous uterine contractions developed but subsided after several hours, at the end of which time a marked drop in serum diastase was observed similar to that found during 3 normal labors (fig. 1). This

patient had a history of 2 previous stillbirths. An elective cesarean section was, therefore, performed and the baby, despite severe cyanosis for a few days, survived. A blood taken 3 days after delivery still showed low diastatic activity.

In the case of *F. M.*, a non-diabetic, the blood pressure at the 30th week had risen from 90/60 to 120/80 mm. Hg and there was also a gain of 5 pounds of weight in the course of one

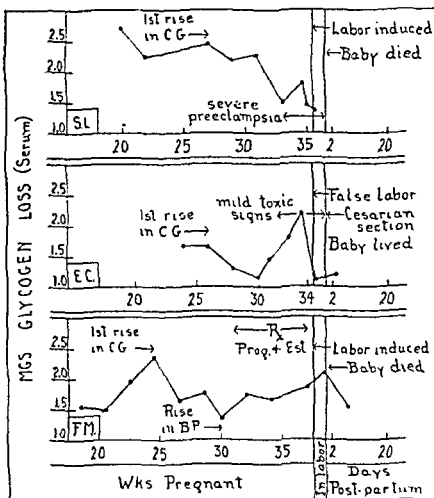


FIG. 2. SERUM DIASTASE IN 3 PATIENTS WITH LATE PREGNANCY COMPLICATIONS. *S. L.*, aged 26, para 1; diabetes for 10 years; controlled by 30 units of insulin daily. *E. C.*, aged 38, para 3; diabetes for 19 years; controlled by 64 units of insulin daily. History of arrested tuberculosis and two previous stillbirths. *F. M.*, aged 30, para 2; non-diabetic. History of premature delivery and stillbirth at 28th week of previous pregnancy.

week. Considering the patient's history of stillbirth with identical clinical signs at the 28th week of a previous pregnancy, together with the steadily rising level of serum chorionic gonadotropin and evidence from urine analyses of a marked deficiency of estrogen and progestin, 5 mg. of estradiol and 25 mg. of progesterone were injected daily, starting at the 31st week, in the hope of averting trouble. Injections were continued for 6 weeks, during which time the serum chorionic gonadotropin dropped to normal levels and the urinary findings reflected an approach toward normal metabolism

<sup>2</sup> The findings on one of these have been reported in detail — *A. L.* of figures 1-6 (ref. 14).

of estrogen and progestin. These changes during therapy were accompanied by a steady rise in the diastatic activity of the serum. Injections were discontinued at 37 weeks, and 4 days later labor was induced. A blood specimen taken at delivery showed increased diastatic activity, a finding duplicated at the time of delivery in *E. H.* (fig. 1), one of the normal cases. The baby died 24 hours post partum. Gross examination of the placenta revealed it to be pale,

after the peak in sex steroid production and conversion. Similarly, in the 3 abnormal cases no drop in serum diastase was observed until after the first indication of hormonal imbalance (that is, the abnormal rise in serum chorionic gonadotropin). In other words, the changes in serum diastase appear to follow rather than accompany shifts in hormone balance. In instances when blood was taken at the time of delivery, and in the only case of severe toxemia a secondary rise in serum diastase was observed.

Aside from the repeated observations on *S. I. E. C.*, and *F. M.*, reported above, a total of 12 analyses for serum diastase were performed upon 8 other women during late pregnancy complications. One had diabetes with premature delivery and stillbirth at 31 weeks. There was no evidence of hormonal imbalance in this individual and 2 blood specimens, one taken a month and the other a week before the accident, revealed no significant change in the level of serum diastase. Of the other 7 patients, all non-diabetic, 2 had severe and 2 mild pre-eclampsia and 3 were eclamptic. No studies were made on these cases prior to the development of toxic signs. The values for serum diastase ranged between 1.37 and 4.37 mg. of glycogen lost from a 20 per cent glycogen solution, using 10 per cent serum dilution. Very high levels were observed in patients from whom blood was taken during convulsions.

As is seen in table 1, the average values in late pregnancy complications are lower than in normal pregnancy before delivery. Considering the wide range over which the values may be distributed, the significance of this difference is questionable. Arneson and Morris (27) found serum diastase values distinctly below normal in 35 per cent of their determinations on patients with pre-eclampsia, and Gray and his collaborators (2) also found subnormal values in toxemia of pregnancy.

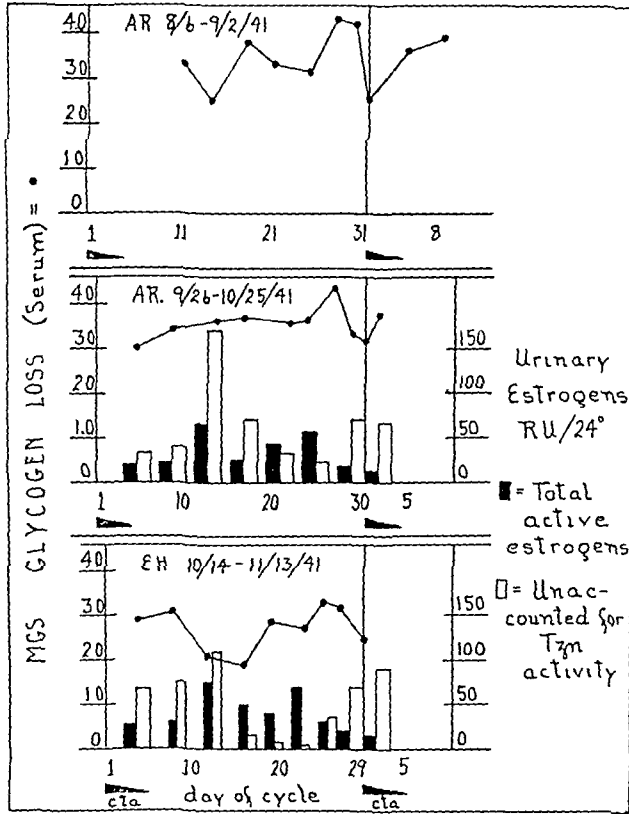


FIG. 3. SERUM DIASTASE AND URINARY ESTROGENS IN MENSTRUAL CYCLES.

firm and thin with many infarcts. Seven days post partum the diastatic activity of the blood had fallen.

Some association between hormone balance and the serum diastase system is definitely indicated by our findings in both normal and abnormal cases. The rise in serum diastase following estrogen and progestin administration to *F. M.* supplies especially convincing evidence in favor of some close relationship between serum diastase and the placental steroids. The data in figure 1 indicate that the peak in diastatic activity in normal pregnancy comes during the last 10 days of gestation, that is,

*Menstrual cycles.* Two women have been studied throughout 3 complete menstrual cycles. Both ovulated regularly, as indicated by their menstrual histories and by repeated studies on the cyclic excretion of estrogens, some of which have been previously reported (15). *A. R.*, aged 28, unmarried, is a case of essential dysmenorrhea and *E. H.*, aged 41, married, is still having normal periods at 27 to 29-day intervals. Urinary estrogens were measured in 2 of the 3 cycles during which repeated bloods were obtained for diastase determinations. In figure 3 the results are tabulated: total active estrogens (that is, estradiol plus estrone plus estriol) being recorded and also

unaccounted for'  $T_m$  activity, an index of the rate of estrogen destruction in the body.

In each of the 3 cycles a premenstrual increase in diastatic activity followed the luteal phase, that is, the period of increased progesterin secretion resulting in maximum conversion and minimum destruction of the estrogens. At the start of menstruation, following estrogen and progesterin withdrawal with the consequent marked increase in the rate of estrogen degradation, a drop in serum diastase was noted. In 2 cycles a drop in serum diastase was also observed at the probable time of ovulation, 14 to 18 days before the start of flow. At this time a peak in the excretion of active estrogens may be noted, but, unlike the second peak during the luteal phase, this early rise is accompanied by evidence of a striking increase in the rate of estrogen degradation, due probably to increased estrogen secretion in the absence of adequate luteal control. It is possible that an intermenstrual drop in serum diastase was missed during the second cycle on A. R. Each urine specimen from this individual represented a 3-day period of excretion and would, therefore, include transient marked changes that might have preceded or followed the moment when the blood was taken.

The luteal phase of the menstrual cycle is analogous to the period in late pregnancy (around the 38th week) when the greatest production and most efficient metabolism of the female sex steroids appears to prevail (13). In both pregnant and non-pregnant women this type of metabolism is followed by a rise in serum diastase. The increased rate of estrogen degradation which characterizes the start of menstruation (10, 15, 19) is also a consistent finding before and during labor (13) and in the late pregnancy toxemias (14), and in each of these situations a decreased diastatic activity of the serum has been observed. In the tabulated results at the probable time of ovulation in E. H. it is particularly indicated that any correlation between the estrogens and serum diastase is more closely related to the rate of estrogen degradation than to the level of secretion or excretion of active estrogens.

The average value for glycogen loss from the sera of these 2 women is higher than those from pregnant individuals (table 1). We question the significance of

this observation, although it is in agreement with those reported by Sugiyama (23, 24) and Goldschmidt-Fürstner (25). Only by averaging a very large number of single observations or by following changes in the serum diastase in a single individual throughout a menstrual cycle, a pregnancy and a confinement could the actual levels during these conditions be compared.

#### DISCUSSION

Considering the number of factors which may influence the diastatic activity of the blood, any interpretation of our data must be purely speculative.

Certain effects of the estrogens upon the secretory activity of the anterior hypophysis have been well established, and our own studies of estrogen metabolism in women have led to the hypothesis that estrogen degradation is an important factor in the growth and maturation of ovarian follicles (13, 15), presumably through pituitary stimulation. Cope, et al., have shown that hypophysectomy causes a sustained increase (6) and the injection of anterior pituitary extract a decrease (8) in the diastatic activity of the blood of dogs. The drop in serum diastase in women, therefore, at the times of increased estrogen destruction, that is, at ovulation, menstruation, before and during labor and in cases of late pregnancy toxemia, might be interpreted as reflecting pituitary stimulation. The increased gonadotropic potency of the urine observed at these times (14, 21, 28, 29) is in keeping with this interpretation, although in pregnancy the gonadotropin is of chorionic rather than pituitary origin. Conversely, the rise in serum diastase following periods of maximum conversion and minimum destruction of the estrogens, that is, after the luteal peak of the cycle and during the last 10 days of pregnancy, might be considered as reflecting decreased gonadotropin secretion due to withdrawal of the stimulus of estrogen degradation.

Adrenalectomy and the administration of adrenal cortical extracts are reported (7) to have even more striking effects upon the diastase system of dogs, the former causing a sustained rise and the latter a fall in the level of this enzyme in the blood. We have previously postulated that the local vascular changes of the menstruating endometrium, as well as the generalized vascular pathology of pre-

eclampsia and eclampsia, may be due to the liberation of some 'toxin' consequent upon an increase in estrogen degradation (14). There is considerable evidence that increased adrenal cortical activity is a normal response to any damaging influence. The drop in serum diastase at the time of ovulation, at the start of flow, in late pregnancy toxemia and just before and during labor would thus be in keeping with the idea that increased steroid degradation supplies some 'damaging influence' which stimulates the so-called (30) adrenal 'alarm reaction.' And the secondary rise in serum diastase observed at the end of labor, particularly when the process is long and difficult, and in the acute stage of severe pre-eclampsia and eclampsia, might be considered as reflecting a degree of cortical exhaustion. We have previously suggested that adrenal exhaustion might contribute to the alarming rapidity with which pre-eclampsia and eclampsia may develop (31).

Direct substitution for cortical secretion by progesterone is another possibility that must be considered in the interpretation of our data. Progesterone in sufficient dosage will prolong the life of adrenalectomized animals (32) and progesterone administration to rats has been shown to cause atrophy of the adrenal cortex (33). Raised titers of serum diastase, therefore, at the times of increased progesterone secretion, as, for example, during the luteal phase of normal cycles and between the 30th and 38th weeks of normal pregnancy, might be accountable to adrenal quiescence as a direct result of progesterone inhibition of cortical secretion. Conversely, the drop in serum diastase at menstruation and labor and in late pregnancy toxemia and the sustained low levels after delivery might reflect increased activity of the adrenal cortex called forth by progesterone withdrawal.

The above considerations are presented merely as possible endocrine factors involved in the observed changes in the level of serum diastase in women. Cope, et al., have noted a species difference between the dog and rabbit in the activity of the serum diastase system (7, 8), and have been unable to correlate any chronic pituitary or adrenal abnormalities in human beings with consistent changes in the level of this enzyme in the blood (17). Further-

more, there is evidence (8) that variations in thyroid activity and in the internal secretion of the pancreas alter the level of serum diastase. These glands may well be influenced by changes in the ovarian and placental hormones inasmuch as they are interrelated with pituitary activity.

Factors other than the endocrines must, of course, be considered in the interpretation of our data. Low diastatic activity of the blood in diseases involving liver damage has been reported (1-5). Heilig and Kantienger (34) have found evidence of impaired liver function at the time of menstruation in normal women, and liver damage is often, if not consistently, a feature of toxemia of pregnancy. There is no indication that liver changes precede the onset of menstruation or the clinical manifestations of late pregnancy toxemia, as do the changes in sex steroid metabolism and the drop in serum diastase, although this possibility cannot be ignored. Gray, et al. (2), have ascribed their finding of subnormal values for serum diastase in pre-eclampsia entirely to impaired liver function.

Finally, there is the well-known influence of the external secretion of the pancreas upon the level of serum diastase to consider. No direct relationship between this and the glands of internal secretion has been established. An increased diastatic activity of the blood has been reported, however, following the injection of acetylcholine into dogs (35), the response being inhibited by previous treatment with atropine. This effect has been ascribed (1, 20) to spastic closure of the pancreatic ducts due to the action of acetylcholine on the parasympathetic nervous system. Reynolds (36) has demonstrated a transient increase in the acetylcholine content of rabbits' uteri following estrogen administration and presents good evidence that the initial hyperemia and vasodilatation of the uterine reaction to estrogen is the result of the acetylcholine-liberating property of this hormone. Our data in women show in most instances a parallelism between the level of estrogen excretion and the level of serum diastase. There are, however, notable exceptions to this generalization. At the time of the first peak in estrogen excretion in the normal menstrual cycle, for example, a drop in serum diastase

was observed. The investigations of Zeller and Birkhauser (37, 38, 39) on the relationship between cholinesterase and the sex hormones suggest that this enzyme, which characteristically destroys acetylcholine, may be increased in those situations in which an increase in the rate of estrogen degradation would prevail. At the time of ovulation, therefore, despite the evidence for an increase in the level of circulating estrogen, liberation of acetylcholine may be overshadowed by an increase in cholinesterase accountable to a temporary increase in the rate of estrogen destruction. All of our data accumulated during the menstrual cycle and pregnancy could thus be interpreted as reflecting an interplay between estrogen conversion and degradation and the production and destruction of acetylcholine with resultant changes in the externally secreting cells of the pancreas. This possible relationship between the course of estrogen metabolism and acetylcholine production and destruction is of particular interest in connection with the local vascular changes of the endometrium during the ovarian cycle (40), the variations in vascular supply to the placenta prior to the onset of labor (41) and the generalized vasomotor disturbances which characterize late pregnancy toxemia.

The composite findings presented in table 1 demonstrate the wide range over which the levels of serum diastase may vary. Only by repeated analyses would changes in activity, under the conditions studied, have been revealed. Furthermore, the alterations in diastase which characterize pancreatic disease appear to be related to acute episodes, normal levels being re-established as the condition becomes chronic (42). Cope, et al. (8), have evidence for a 'compensatory mechanism' in the serum diastase system of dogs, and in the case of our patient, S. L., a severe pre-eclamptic, the rise when the patient became alarmingly ill was transient in nature. These considerations emphasize the importance of repeated analyses as against single observations in the study of diastatic activity.

#### SUMMARY AND CONCLUSIONS

Diastatic activity was measured in 98 specimens of blood from 22 women during the last

10 weeks of pregnancy, labor and the puerperium. There were 11 normal pregnancies, 6 cases of pre-eclampsia, 3 eclamptics and 2 cases of fetal death. The findings are compared with changes in estrogen metabolism during these episodes.

Twenty-nine analyses were performed upon blood from 2 women throughout 3 complete menstrual cycles, during 2 of which urinary estrogens were determined.

Repeated analyses indicated a rise in serum diastase after the 30th week of normal pregnancy to a peak within 10 days of delivery, a drop just before and during labor, and low values for as long as 1 month post partum. A progressive decrease preceded and accompanied those late pregnancy complications associated with imbalance of the placental hormones, this effect being counteracted by estrogen and progesterone administration and by self-correction of the steroid deficiency.

In women with normal menstrual cycles a rise in serum diastase during the luteal phase reached a peak a few days before the onset of flow. Menstruation was preceded and accompanied by a precipitous drop. In two instances there was a drop at the probable time of ovulation.

In both pregnant and non-pregnant women, the decreased rate of estrogen degradation which characterizes increased progestin secretion was followed by a rise in serum diastase, whereas a drop in enzymic activity was associated with evidence from urine analyses, of increased estrogen degradation due to progestin withdrawal or deficiency.

Possible endocrine interrelationships to account for these findings are discussed.

The co operation of the following physicians in procuring the material for this investigation is acknowledged: Doctors D. Hurwitz, S. B. Kirkwood and F. S. Kellogg, of the Boston Lying-in Hospital.

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# Treatment of Menstrual Disturbances in Adolescent Girls

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MENSTRUAL disturbances in adolescence consist of two varieties, those of rhythm and those of amount and duration of bleeding. Both types of disturbance usually are temporary since ultimately the girl's own ovaries mature sufficiently to establish normal menstrual rhythm and flow. While menstrual irregularity presents no clinical problem, excessive or persistent bleeding does require medical intervention. Two distinct therapeutic approaches have been successfully employed in such cases, but each has serious disadvantages. When the bleeding is of serious proportions, surgical treatment, i.e., curettage and packing of the uterus, and even laparotomy for excision of ovarian cysts has been undertaken. It is obviously undesirable to submit patients to the risk of anesthesia and operation upon the genital tract if some way of avoiding it is available.<sup>2</sup> For less serious bleeding, male sex hormone in large doses has been successfully used; this therapy involves the risk of inducing such masculinization as acne, hirsutism, hoarseness of voice and enlargement of the clitoris.

The disadvantages of the methods for treating menorrhagia noted above, coupled with the scattered reports of successful therapy of this condition with progesterone and estrogen, led us to investigate systematically a series of patients complaining of severe, irregular bleeding. It was hoped that with the vaginal smear technic (1, 2) as a guide, we could infer whether the bleeding occurred from an atroph-

ic or from a hyperplastic endometrium. The rationale of therapy was to be the induction of a), endometrial proliferation with estrogens, if the bleeding was from an atrophic endometrium or b), a transformation from a hyperplastic to a secretory endometrium with progesterone, if the bleeding was from a presumably hyperplastic endometrium.

The vaginal smear which indicates the presence of a hyperplastic endometrium consists of plaques of cornified epithelial cells (*type IV*); the vaginal mucosa, in response to high and persistent levels of estrin, has grown so thick that its superficial cells (from which the vaginal smears are taken) are partially keratinized and degenerated (fig. 1). In contrast the vaginal smear which accompanies an atrophic endometrium consists of basal epithelial cells (*type VIII*) which are small and round with large vesicular polychromatic nuclei (fig. 2). Either through refractoriness of the end organ, or because there is an absolute lack of estrogen, the vaginal mucosa has remained thin so that cells from its superficial layers are the actively dividing and growing cells; i.e., basal cells. Each of these smear types is so distinct from that occurring normally during menstruation, that no difficulty should be encountered in making the differentiation. The normal vaginal smear at the time of menstruation contains blood, cells and cell fragments (*types VII, I, II*) from the vaginal epithelium which is neither atrophic nor hypertrophic; that is, the cell nuclei show only early evidences of pyknosis while the cytoplasm is somewhat granular and frequently folded. By keeping in mind these three distinct vaginal smear types it is relatively easy to determine whether any particular episode of bleeding is normal or pathologic, and if the latter, whether it occurs from an atrophic or hyperplastic endometrium.

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<sup>2</sup> This report does not imply that the use of male sex hormone to ovariolectomized animals means V; it does not require surgery.

In those of our cases in whom a highly cornified vaginal smear was found (indicating a hyperplastic endometrium), progesterone was used to convert the hyperplastic endometrium to the secretory type and thus stop the bleeding. It was to be expected that upon interruption of progesterone therapy a normal and self-limited menstruation would occur. It is important to remember this, for progesterone-withdrawal bleeding should not be mistaken for a

tion, consisting of cell types *VII*, *IV*, *III*. The continued, however. A week later the smear was that of hyperestrinism (*types IV*, *III*) and suggested a recurrence of menometrorrhagia from a hyperplastic endometrium. Progesterone<sup>3</sup> in 10 mg. doses was injected on 5 consecutive days (total 50 mg.). On the 5th day bleeding stopped. Two days after stopping progesterone therapy, bleeding recurred, but subsided gradually and stopped entirely 5 days later. The patient has since had 9 normal periods with intervals of 4 to 5 weeks. There has been no recurrence of menometrorrhagia.

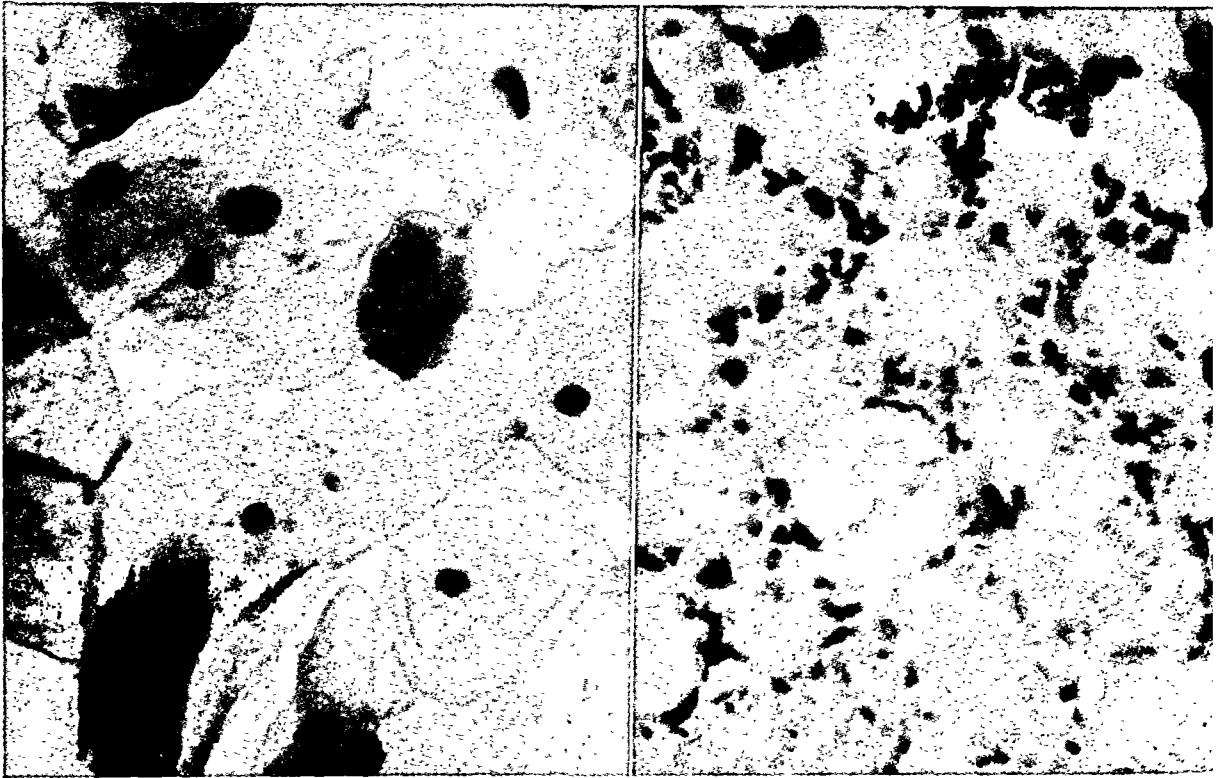


FIG. 1, left. Vaginal smear consisting of plaques of cornified epithelial cells (*type IV*).

FIG. 2, right. Vaginal smear consisting of basal epithelial cells (*type VIII*), which are small round cells with large vesicular polychromatic nuclei.

recurrence of metrorrhagia. An example of this type of case follows:

#### CASE REPORTS

The patient, a 14-year-old girl, menarche at 12 years, was first seen in the Clinic because of profuse bleeding of two weeks' duration. Vaginal smears consisted of plaques of cornified cells (*type IV*) resembling the smear shown in figure 1, plus an abundance of red blood cells. She was given pregnenolone<sup>3</sup> (oral progesterone) 10 mg. per day for 14 days. The bleeding subsided, but did not stop. When therapy was interrupted bleeding again became more profuse, threatening to exsanguinate the patient. The vaginal smear now seemed more nearly normal for menstrua-

In this patient and in three others with similar histories and findings it has been possible to interrupt the episodes of severe bleeding by means of adequate progesterone dosage, as illustrated by the following case histories.

*Case 2*, a negro girl, aged 12, was seen in her 1st menstrual period, 9 months after menarche. The period was excessively profuse and was continuing beyond 8 days. The developmental history was normal. No abnormalities of body size or shape were noted. Rectal examination revealed a uterus of normal size with a firm, erect corpus. The adnexae were not palpable. The Hb was 60 per cent; erythrocytes, 3.8 million; leucocytes, 8.6 thousand with a normal differential count. Vaginal-smear cell types *IV*, *III*, and *VII* were found. Testosterone propionate in 25 mg. doses was given and repeated at 2-day intervals until

<sup>3</sup> Pregnenolone (Lutocylin) and progesterone (Lutocylol) were supplied by the Ciba Pharmaceutical Products, Inc.; Summit, N. J.

100 mg. had been injected. Bleeding stopped in one week. The vaginal-smear cell types were *III*, *III*, *II*, *I*. She returned 33 days later with a recurrence of profuse bleeding. Progesterone, 10 mg. per day for 5 consecutive days was given and the bleeding stopped. A single 'gush' of blood occurred the day after cessation of progesterone therapy. Spotting continued 4 days longer. She has had 4 normal menstrual periods since the last treatment.

*Case 3*, a white girl, aged 11 years, was seen on the 22nd day of profuse menstrual bleeding which required the use of 12 sanitary napkins per 24 hours. Menarche had been at 9½ years of age. The menses had been irregular in interval and duration since their onset. The girl appeared older than her stated age, with large breasts and adult external genitalia. She was somewhat obese, but pale and weak. The Hb was 50 per cent, erythrocytes 3.3 million. Rectal examination disclosed a large, boggy uterus characteristic of that in the premenstrual phase of a normal adult woman. Vaginal smear showed cell types *IV*, *VII*. Progesterone, 5 mg. b.i.d. was given until bleeding stopped, requiring a total dose of 30 mg. There were some mild cramps and spotting for 2 days following interruption of therapy, then 5 days of 'normal' menstruation requiring the use of 6 to 8 pads per day. Bleeding stopped spontaneously on the 8th day. The next menstrual flow began 23 days later, and was so profuse as to frighten the patient and her mother. She was again given progesterone intramuscularly, 5 mg. b.i.d. until a total dose of 25 mg. was given. The bleeding diminished during the therapy, spotting continued for 3 days after interrupting the injections. The patient has since had 3 normal menstrual periods.

*Case 4*, a negro girl 12 years old, whose menarche had occurred a year before, was seen during her second episode of menorrhagia. She had had curettage (at which time a hyperplastic endometrium was found) 4 months before. The vaginal smear was type *IV*, *VII*. She was given anhydroxy-progesterone tablets, 10 mg. t.i.d. for 7 days. At that time the vaginal smear was type *VII*, *IV*, *V* and the bleeding had diminished. An endometrial biopsy showed 'presecretory' endometrium. The medication was continued for 3 days longer, and the bleeding stopped entirely. A moderate flow recurred 6 days later and continued, in diminishing amounts, for 5 days. The vaginal smear was type *VII*, *III*, *II*, *V*. No further bleeding occurred for 6 weeks, then a normal period occurred. Thirty-two days later menorrhagia began again. It was interrupted by injections of progesterone, 10 mg. per day for 5 days. Moderate withdrawal bleeding followed interruption of therapy. There has been no recurrence of menorrhagia in 3 months since the last therapy.

It is not claimed that progesterone will effect a cure, but it may be used to tide the girl over a period until the girl's own ovaries begin their cyclical secretion of progesterone. In our experience, 50 mg. of progesterone distributed

over a 5-day interval, has been the only consistently effective therapy. The effectiveness of oral progesterone in doses as high as 30 mg. per day for 10 days has not equalled that of 50 mg. of injected progesterone.

Bleeding due to hypoestrogenism occurs occasionally. The bleeding starts at the time of a normal menstruation but fails to stop. Whereas, in the normal girl, bleeding stops upon reconstitution of the endometrium under the influence of estrogen, in these patients there is a delay in reconstitution of the endometrium. The stimulus to growth (estrogen) is either inadequate or lacking. The bleeding, therefore, continues indefinitely until some stimulus to healing is provided. In such patients the vaginal smear offers characteristic criteria. It resembles that of the normal prepubertal girl. The epithelial cells are from the basal layer, small, round cells with large vesicular nuclei. When such a smear is encountered in a persistently bleeding patient past the menarche, the logical therapy would seem to be to stimulate the proliferative and reparative processes in the endometrium by giving estrogen. The following case history provides a typical example.

A 15 year old girl, menarche at 12 years, was brought in by her mother, who reported that bleeding and spotting had occurred continuously and persistently for the past 7 months. During all of this time the girl had had to wear sanitary napkins and had been advised to refrain from sports and exercises. She was moderately anemic. Her growth and appetite were normal. The persistent bleeding was not only a source of worry, but was a drain upon the hemoglobin and iron. Rectal examination revealed no pelvic abnormalities. The external genitalia were normal. The hymen was intact. The vaginal smear consisted of blood, leucocytes, and basal (type *VIII*) cells. She was given 0.1 mg. of stilbestrol orally each day. In 3 weeks the bleeding stopped. Stilbestrol therapy was continued for 6 weeks longer and then was gradually tapered off, one tablet being given on alternate days and then every third day. Normal menstrual periods occurred during the course of treatment. In the following 6 months, periods have recurred at regular intervals and the patient has been free from menorrhagia.

*Case 6* was a 12 year old girl at menarche. This, her first menstrual period, had begun 3 weeks previously as a moderate flow, but spotting had persisted since. Developmental history and physical examination revealed no abnormalities. The Hb was 75 per cent. The

\*The stilbestrol was supplied through the courtesy of Dr. E. Gifford Upjohn, The Upjohn Co., Kalamazoo, Mich.

blood count showed 4.2 million erythrocytes, 8.2 thousand leucocytes with a normal differential count. The vaginal smear showed cell types VII, VIII, I. She was at once given an injection of 1 mg. of estradiol dipropionate<sup>5</sup> and 0.12 mg. of stilbestrol<sup>6</sup> was prescribed to be taken each night before retiring. Bleeding stopped in 10 days. The vaginal smear types were VII, II, I. She continued the same medication until 4 mg. had been taken. Three weeks later a normal period began; 4 mg. of stilbestrol in 0.12 mg. doses in liquid form<sup>6</sup> was again prescribed. A 'brownish' vaginal discharge persisted for 10 days after the 4-day normal menstruation. She has had no further therapy, and there has been no recurrence of menorrhagia in 9 subsequent menstrual periods.

Case 7 was a 13-year-old girl, whose menarche had occurred at 11 years. The history revealed Pott's disease which had healed without deformity after appropriate treatment. This was the 5th day of the 3rd episode of menorrhagia, which in this patient began as a 'normal' period with profuse flow on the second and third days, tapering off to a flow requiring about 4 napkins per day for 10 to 12 days more. Vaginal smear cell types were VII, I, VIII, V. She was given stilbestrol, 0.5 mg. per day. In one week the vaginal smear showed cell types III, VII, II, IV. The dosage of stilbestrol was reduced to 0.1 mg. per day, and therapy continued. Bleeding stopped on the 10th day; this may have been a coincidence. Stilbestrol was continued at 0.1 mg. per day for a total of 100 days. She had 2 normal menses during the period of therapy. Therapy was then interrupted. She has continued to have normal menstrual periods every 4 to 5 weeks for nearly a year.

#### DISCUSSION

While, in general, control of menometrorrhagia, regardless of its etiology is possible by surgery or by giving large doses of male hormone, these types of therapy are undesirable for the reasons previously outlined. The problem was therefore investigated from the point of view of possible treatment with one or another of the female sex hormones. This proved possible since the vaginal smear permitted determination of the cause of the bleeding. Classical methods such as endometrial biopsy, curettage, or hormone assays are laborious and expensive, and may involve invasion of the genital tract, while the vaginal smear technique

is rapid, easy, and acceptable to the patient. The difference between the cell types in normal menstrual smears and in the smears obtained respectively, from cases of hyperestrinism and hypoestrinism are so characteristic as to lead to no doubt concerning the diagnosis.

Thus, in three patients (ages 12, 13, 14) whose vaginal smears showed the presence of basal epithelial cells, indicating an atrophic endometrium, the bleeding was controlled by estrogenic therapy. And in the four patients (ages 11, 12, 12, 14) whose vaginal smears were predominantly plaques of cornified epithelial cells with pyknotic nuclei, progesterone therapy controlled the bleeding. It should be emphasized that upon withdrawal of progesterone therapy bleeding occurs. This bleeding, in contradistinction to the bleeding for which therapy is given, is self-limited and resembles that of a normal menstrual period. The use of progesterone should not be discarded simply because bleeding recurs upon withdrawal; such bleeding is expected.

While cases of menometrorrhagia are not very frequent in pediatric practice, when they do occur they present serious problems. The diagnostic aid obtained by use of the vaginal smear technique allows definitive diagnosis and treatment on the basis of etiology. The treatment may be continued until such time as the patient's own ovaries mature sufficiently to prevent the recurrence of menometrorrhagia.

#### SUMMARY

Seven patients, aged 11 to 15 years, presenting the complaint of severe and/or prolonged menstrual bleeding were studied by the vaginal smear technique. On the basis of the cell types in the smears, it was possible to separate the cases into two groups: the one to be treated with estrogen, the other with progesterone.

The bleeding in all patients was successfully controlled by the appropriate therapy.

I am glad to acknowledge the advice and criticism of Dr. S. Soskin, Director of the Department of Metabolic and Endocrine Research.

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<sup>5</sup> Estradiol dipropionate (Di-ovoclyn) supplied through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, N. J.

<sup>6</sup> Stilbestrol (Elixir Stilbestrol) 1 mg. per fluid ounce was supplied through the courtesy of Dr. E. Gifford Upjohn, The Upjohn Co., Kalamazoo, Mich.

# A Case of Secondary Amenorrhea

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THE RESULTS of treatment of secondary amenorrhea are often a source of dissatisfaction both to the patient and her physician. We are reporting a case of secondary amenorrhea in which a careful diagnostic survey was completed and an unusually long and tedious course of therapy was given before a completely successful result was achieved.

## CASE REPORT

The patient was first seen in March, 1941, at the age of 17. She was a thin, pale, white schoolgirl who had not had a menstrual period since June, 1940. Menarche occurred at 13 years of age. She had her first 3 periods at 6 month intervals and then had regular 6 week menstrual cycles which terminated abruptly in June, 1940. Her periods had been normal in duration and were never painful. She had never been operated upon and had had only the usual childhood diseases.

**Physical examination.** Physical examination revealed a thin, white girl with no endocrine stigmata. The weight was 103 lb., height, 62 inches. The anthropometric measurements were normal. The breasts, external genitalia and hair development were of normal appearance. She was mentally alert but phlegmatic. With the exception of a deviated septum and nasal polyps, the examination revealed no abnormalities. A vaginal examination was not made because of an unruptured hymen, but a rectal examination showed that the pelvis was normal except for an unusually small, hard uterus which was in the normal anteverted position.

**Laboratory data.** Temperature, pulse and respiration were normal. The blood pressure was 104 mm. Hg systolic, 62 diastolic. Blood and urine examinations gave values within the range of normal. The basal metabolic rate was minus 1. A vaginal smear indicated a *Grade III* reaction of the vaginal mucosa. The Wassermann reaction was negative. The sugar tolerance was high, a flat curve was obtained after the ingestion of 100 gm. of dextrose. Roentgenograms of the sella turcica revealed no abnormalities. The visual fields were en-

tirely normal. Two gonadotropic hormone investigations of 48 hour urine collections were made by the tannic acid precipitation procedure of Levin and Tyndale and assayed using the immature mouse uterine weight method. The urine specimens were collected one week apart and both yielded less than 10 mouse uterus units per 24 hour collection. Three assays for daily urinary estrogens were made by Kurzrok's method. They showed an average of 5 rat units per liter.

**Treatment.** The patient was first given a series of injections of estrogen in an attempt to increase the size and responsiveness of the womb. Ten injections, each 0.33 mg. of estradiol benzoate<sup>1</sup> were given in 3 weeks. These were followed immediately by daily injections for 5 days of 10 mg. of progesterone.<sup>1</sup> The patient bled for 4 days, the flow beginning 54 hours after the last injection of progesterone. Two weeks after the last day of vaginal bleeding, she was given a second series of 5 progesterone injections without preliminary estrogenic medication. Sixty five hours after the final injection, a flow began which lasted for 3 days. A third and identical series of progesterone medication was given two weeks later without a preceding course of the estrogens. This did not produce vaginal bleeding.

The patient was permitted to go without medication for 6 months during which time she did not menstruate again. In November, 1941, she was given a course of 'stimulative' roentgen ray exposures to the pituitary gland and ovaries. She received 600 r to the right temporal region and 400 r to the left temporal region in 5 exposures. The ovaries received 8 irradiations during one month. 300 r to the right anterior pelvis and 300 r to the left anterior pelvis. The pituitary irradiation factors were 200KV, 4 ma,  $\frac{1}{2}$  Cu plus 1 Al filter. The pelvic factors were 200 kV, 4 ma, 1 Cu plus 1 Al filter. All treatments were given at 50 cm. These treatments did not result in any further bleedings, although she suffered a temporary alopecia about her temples.

Two months after the last roentgen exposure, the patient was started on 3 courses of combined oral estrogen and progesterone medication. Each course began with daily doses of 10 mg. of stilbestrol for 10

<sup>1</sup> The estradiol benzoate (Dimenformon Benzoate) progesterone (Progestin) and the pregnenolone (Progestoral) were supplied by Dr. Leo Pirk of Roche Organon Inc., Nutley, N. J.

days and was immediately followed by daily doses of 70 mg. of pregnenolone<sup>1</sup> for 5 days. The interval between the courses of therapy was approximately 3 weeks. Each series of oral medication resulted in an adequate vaginal bleeding. The last flow occurred on March 25, 1942.

The patient menstruated spontaneously in April, 1942, and has menstruated at 6-week intervals, without medication, up to the present time (October, 1942). The menstrual periods are of satisfactory duration and intensity. It is interesting that she has reverted to the 6-week intermenstrual interval exhibited before amenorrhea had become established. She is still at school, does approximately the same amount of work and has not had any unusual economic changes.

#### SUMMARY

Two uterine bleedings were induced in a young schoolgirl with secondary amenorrhea of 8 months' duration by the parenteral use of progesterone. A spontaneous, normal, menstrual rhythm was not produced. A series of so-called 'stimulation' roentgen exposures to the pituitary and the ovaries was unsuccessful in establishing menstruation. A third series of therapeutic attempts using the combination of stilbestrol and pregnenolone orally was followed by menstruation recurring spontaneously at 6-week intervals.



# Vaginal Smear Technic

[[A Review Article]]

Its Use in the Diagnosis of Ovarian Failure,  
as an Index to Efficacy of Endocrine  
Therapy and as a Human Assay Method

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THE VALUE of the vaginal smear method for the study of ovarian functions is based upon the response of the vaginal epithelium to the hormones of the ovary. This relationship has been long evident from comparison of the structure of the undeveloped vagina in childhood and the atrophic mucosa of senility with the histologically normal, fully developed epithelial structure characteristic in sexual maturity, it has more recently also been indicated by the apparent occurrence of rhythmic alterations of the vaginal epithelium during the menstrual cycle. These changes have been accepted by many as proof of a human vaginal cycle. Papanicolaou's publication in 1933, supporting this belief, indicated that such cyclic variations could readily be demonstrated in stained smears of human vaginal fluid (1). A later publication, with Shorr in 1936, described the vaginal cytology of the menopause and advocated the vaginal smear method for the diagnosis of ovarian failure, at the same time demonstrating clearly the morphologic transformation of the vaginal fluid following adequate estrogen therapy (2).

The potential importance of this simple means for investigating ovarian functions and failures, and its evident practical value in gauging therapeutic responses was at once apparent. The following critical review is presented in an effort to appraise the usefulness of the vaginal smear method as judged from pertinent publications in the available literature.

## VAGINAL SMEAR TECHNIQUES

Since the original method for obtaining and staining vaginal smears was described by

Papanicolaou, several modifications of technic have been proposed to simplify this procedure. The technical details and the microscopic features of the various staining methods are summarized briefly.

### *Ehrlich's Hematoxylin-Eosin-Water Blue Stain (Papanicolaou, 1)*

**Technic** Secretion obtained from the vagina by means of a curved glass pipette is spread upon glass slides which are immediately immersed in a jar containing equal parts of 95 per cent alcohol and ether. After fixation ( $1\frac{1}{2}$  to 1 hour) the smears are stained with hematoxylin, eosin and water blue in the following manner:

Slides are first stained with Ehrlich's hematoxylin for about 5 minutes, then carried into running water for at least a quarter of an hour. After this, they are stained with a 0.5 per cent eosin for about 3 to 4 minutes, rinsed well in water, and finally stained for 1 minute in a 0.5 per cent solution of water blue. Following this they are rinsed well in water and then carried through 50 per cent, 70 per cent, 80 per cent, 95 per cent and absolute alcohol into xylol and mounted in Canada balsam. The stain is permanent and does not fade easily.

**Microscopic appearance** The author describes the preparation as follows:

This secures a sharp outline of the various cell types with a variety of shades from an intense blue to an eosin red. The cornified cells, which are almost constantly present in the vagina, take an intense eosin color and are sharply differentiated. On the other hand, cells derived from the deeper vaginal layers, which are free from cornification, are stained strongly blue. Partly cornified cells show various shades of purple. Superficial secretory cells, containing mucus, display a typically characteristic bluish purplish tone. Leucocytes, as well as bacteria, are also sharply outlined. Eosinophiles show distinctly red granulation. Mucus takes a bluish or purplish shade. The contrasts are sharper than with ordinary hematoxylin-eosin and the cornified cells are particularly differentiated. This is important for the vagina, in which the cornification is very pronounced, especially during certain periods of the cycle.

### *Modified Masson Trichrome Stain (Shorr, 3)*

**Technic** The vaginal secretion, aspirated by means of a dry pipette with rubber bulb attached, is expelled

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onto a glass slide. While still wet, the slide is fixed in equal parts of ether and 95 per cent alcohol. Fixation for 1 or 2 minutes is adequate. Instead of imported stains (Ponceau de Xylidene and Light Green) Shorr later substituted domestic Biebrich Scarlet and Fast Green FCF for staining.

(1) From fixing solution, carry through alcohols to water; stain with Harris' hematoxylin for 2 minutes, and wash in running water for 5 minutes. (2) Instead of the Ponceau de Xylidene-Acid Fuchsin-Orange G solution, 1 per cent Biebrich Scarlet, water soluble (Nat'l Aniline and Chem. Co.) and 0.4 per cent Orange G in 1 per cent acetic acid. Stain 1 minute and rinse in water. (3) In place of the 3 per cent phosphotungstic acid mordant, a mixture of equal parts of 5 per cent phosphomolybdic and phosphotungstic acids. Mordant 1 minute and rinse. (4) In place of 0.3 per cent Light Green, a 0.25 per cent solution of Fast Green FCF (Nat'l Aniline and Chem. Co.) in 0.3 per cent acetic acid. Stain 2 minutes. Do not rinse. (5) Differentiate in 1 per cent acetic acid for 1 minute, carry through alcohols to xylol and mount in damar.

A single differential stain incorporating all the components of the trichrome method described above, with the exception of hematoxylin, was recently recommended by Shorr for clinical investigations (4). The greatly simplified technic is as follows.

1. Aspirate the vaginal secretion by means of a dry pipette with rubber bulb attached, and expel onto a glass slide. 2. Fix, while wet, in equal parts of ether and 95 per cent alcohol. Fixation for 1 or 2 minutes is adequate. 3. Stain for approximately 1 minute in Solution S3. 4. Carry through 70 per cent, 95 per cent and absolute alcohol, dipping slide 10 times in each solution. 5. Clear in xylol and mount in damar.

The composition of the single differential stain (S3) is as follows:

ethyl alcohol (50 per cent).....	100.0	cc.
Biebrich Scarlet (water sol.)...	0.5	gm.
Orange G.....	0.25	gm.
Fast Green FCF.....	0.25	gm.
phosphotungstic acid c.p.....	0.075	gm.
phosphomolybdic acid c.p.....	0.5	gm.
glacial acetic acid.....	1.0	cc.

*Microscopic appearance.* Shorr describes the results as follows.

It provides a sharp differentiation between cornified and non-cornified elements. The former stain a brilliant orange-red; the latter take on a green stain which is deeper in the younger cells, and paler in those more advanced. The staining is delicate and reveals cytoplasmic and nuclear details very clearly. Other constituents, such as leucocytes, erythrocytes, bacteria and spermatozoa, are satisfactorily differentiated.

*Fuchsin Stain (Salmon and Frank, 5; Geist and Salmon, 6:)*

*Technic.* The procedure is described by the authors (6).

A speculum is inserted into the vagina and the vaginal mucous membrane and cervix inspected to exclude the presence of any infection. A small amount of the vaginal secretion is aspirated from the surface of the posterior blade of the speculum with a small glass pipette. The secretion is diluted with a little normal saline, spread on a glass slide, allowed to dry in the air and stained for one minute with fuchsin; the smear is then washed with tap water and is ready for examination.

*Reagent:* 1. Fuchsin..... 3.0 g  
Alcohol 95 to 100%..... 100.0 cc  
2. Alcoholic fuchsin (1)..... 12.0 cc  
Distilled water..... 100.0 cc

*Microscopic appearance.* Estrogen deficiency is recognized by the presence of small, round or oval epithelial cells with large, darkly staining nuclei (atrophic cells). The normal smear consists of large, flat, clean outlined, squamous cells with small, deeply staining nuclei. Details of the smear types observed in menopause and following estrogen therapy, as described by Geist and Salmon, are included below in discussion of vaginal smears in the menopause.

*Modified Best's Carmine Stain (Salmon, Walter, and Geist, 7)*

*Technic.* The authors write:

Patients are instructed to take a plain water douche evening the smears are taken. A speculum is inserted into the vagina and the cervix and fornices are wiped clean. The speculum is then withdrawn, at the same time sweeping off the secretion from the anterior wall with the posterior blade of the speculum. The secretion on the blade is then diluted with an equal part of normal saline and spread on a glass slide. Fixation is obtained by drying in air. A modification of Best's carmine stain (which is used in the Department of Pathology of the Mt. Sinai Hospital to demonstrate glycogen in tissues) was adapted for the smears.

1. Stain with hematoxylin for 5 min.
2. Rinse in cold water.
3. Stain with carmine solution for 15 min.
4. Differentiate in  
Absolute ethyl alcohol, 16 cc.  
Absolute methyl alcohol, 8 cc.  
Distilled water, 20 cc.  
Immerse 4-5 times.
5. Absolute alcohol—2 immersions.
6. Xylol—2 immersions.
7. Mount with balsam.

*Microscopic appearance.* The appearance of the preparation is described by the authors.

The glycogen appears as deep red granules in the cytoplasm. In some cells the granules are coarse, while in others they are so fine that their cytoplasm is diffusely pink. The nuclei stain blue. This stain also reveals distinctly the morphologic characteristics of the cellular elements of the smear. . . Smears taken throughout the menstrual cycle (except during the period of actual menstruation) in women with regular cycles show slight variations in glycogen content which are difficult to interpret. In some women the smears are uniformly lower in glycogen content than in others. This phase of the problem will be reported on later.

*Iodine Vapor Stain (Mack, 8)*

*Technic.* 1. *Preparation of smears.* A cotton applicator is inserted into the vagina and twirled lightly (one complete rotation) against the vaginal wall. The cotton end of the applicator is then rolled lengthwise over the surface of a clean glass slide. By rolling, rather than rubbing, a uniformly thin film of cells, with minimal clumping and cell distortion, results. The film dries almost immediately and may be stained at once.

2. *Staining of smears.* Staining is accomplished simply by laying the slide, face down, over a shallow dish containing a small amount of Lugol's solution. Iodine vapors which arise

insensibly from the solution suffice to stain the glycogen containing cells in two or three minutes. Microscopic examination may be carried out immediately. Although such stains fade in 24-28 hours, re staining (by the same method) may be carried out repeatedly if later examinations are desired.

**Microscopic appearance.** Vaginal smears with normal glycogen content are recognizable even macroscopically by the great preponderance of large, flat, polygonal cells with rich brown or violet brown cytoplasm. The unstained nuclei (recognizable as small, translucent, round bodies) are located in the central portions of the cells. Varying numbers of smaller and more rounded cells taking a deep brown color are also found with some degree of regularity. In contrast to the iodophilic brown cells, a large number of non glycogenic, unstained or lightly stained lemon yellow cells of irregular size and shape and poorly defined borders, make up the balance of the normal picture. The latter are the totally cornified squamous cells from the surface of the mucous membrane. For practical purposes, with this method identification and classification of cell types is unnecessary. The vaginal smear of the normal cyclic woman is recognizable by the preponderance of deeply and uniformly stained brown iodophilic cells.

Smears taken from women during various stages of the menopause as well as from young children prior to puberty are distinguishable macroscopically by the absence of the rich brown color of the stained smear. Such slides have a lemon yellow, buff, brownish yellow, or light brown appearance depending upon the degree of glycogen poverty. In extreme grades of vaginal atrophy, as in very young children, or in advanced stages of the menopause, smears consist almost entirely of leucocytes, amorphous debris, and varying numbers of yellow superficial squamous cells. In less advanced stages of ovarian hypo-function (as in earlier phases of the menopause and in pre-pubescent children) minimal glycogen content is discernible by the presence of mottled cells, i.e. cells containing small, irregularly distributed brown deposits at the cell margins and in the cytoplasm. The brown color rarely involves the entire cell as in sexual maturity. The cells in glycogenic smears are generally smaller in size and more rounded in form and have their origin in the deeper layers of the epithelium. Unstained, irregularly shaped cells, typical of the superficial cornified layer are present in abundance. They too appear to be smaller than in normal smears.

As is evident from the foregoing, the original staining methods of Papanicolaou and of Shorr are complicated procedures practicable chiefly for the use of research workers with skilled technical assistance. Shorr's 'single differential stain' seems to provide fewer technical difficulties. The fuchsin and the iodine vapor stains are best adapted for clinical investigations with limited laboratory facilities. The iodine vapor method depends upon a specific color reaction for glycogen alone, places less dependence than other technics upon the cytologic features of the smear, and, hence, requires less microscopic skill and experience.

#### VAGINAL SMEARS IN THE NORMAL MENSTRUAL CYCLE

Papanicolaou's exhaustive study to date remains the only detailed description yet offered

of the normal cycle as revealed in vaginal smears. Briefly summarized, these changes in a typical 28-day cycle are as follows:

**Menstrual phase (1-7 days)** Erythrocytes, fibrin, bacteria and squamous cells of the superficial or intermediate types; large numbers of leucocytes appear at the end of this period as the erythrocytes vanish.

**Follicular or copulative phase (8-12 days).** Leucopenia, increase in mucus. The epithelial cells are of the superficial or intermediate types with an increasing tendency to cornification, the cornified cells are usually nucleated.

**Ovulatory stage (12-13 days, usually)** Sudden increase in leucocytes and decrease of mucus. Nucleated cornified cells abundant. Return of erythrocytes indicates ovulatory bleeding.

**Post-ovulatory or proliferative phase (13-17 days)** Variable proportions of leucocytes and cornified cells.

**Secretory or premenstrual phase (18-28 days)** Abundance of cells and leucocytes. Most cells of superficial type with larger nuclei, decrease in numbers of nucleated cornified cells, rich mucus consistency. With approaching menstruation, erythrocytes, and cell plasmolysis and fragmentation produce a pronounced irregularity in the structures of the smear.

For full details of the cytologic variations occurring in the normal vaginal cycle the reader is referred to Papanicolaou's publication. A careful study of the text of this exhaustive report leaves little doubt as to the probable existence of a histologic cycle as has also been shown (notably by Dierks) by histologic methods. Full accord as to details and extent of these changes has, however, not been reached among investigators of this subject. Hence, until more extensive studies of these cyclic alterations manifested in vaginal smears completely substantiate Papanicolaou's descriptions, his findings must be taken with some reservation. It is obvious, from the bizarre and varied cytologic patterns described, that more than ordinary microscopic skill and experience is necessary to conduct such investigations. Accordingly, it seems evident that the vaginal smear method for investigating normal vaginal physiology is the province solely of the expert histologist.

#### VAGINAL SMEARS IN CASES OF OVARIAN FAILURE

##### *Menopause*

In contrast to the cyclic changes of the vaginal epithelium, which are slight in degree and difficult to interpret, the cytologic characteristics of the atrophic mucosal smear are

striking and more easily recognized, especially in advanced senility and following castration. In advanced atrophy, smears consist of numerous compact, round or oval cells which stain deeply and contain large round or oval, well-preserved nuclei. These are known as 'deep cells' since they are derived from the deeper layers of the vagina; large superficial cells from the uppermost layers are present in small numbers. Leucocytes are also numerous and erythrocytes are frequently found. Smears of this type offer no great difficulties of interpretation to the casual microscopist.

When atrophy of the vagina is less pronounced, however, smears display a high degree of variability. Superficial cells are more numerous, while deep cells may vary in number from great abundance to complete absence. In addition, the cells show an absence of uniformity of outline and structure, they tend to form irregular clumps, and show poor preservation of cytoplasm and nuclei. The presence of large numbers of bacteria gives to the smear a 'dirty' appearance. Papanicolaou and Shorr attribute the great variability in part to the spontaneous re-appearance of rhythmic, cyclic changes. They describe 6 prevailing types of postmenopausal smears: *a*) The menopausal atrophic type; *b*) the intermediate type; *c*) the mucous type; *d*) the premenstrual type; *e*) the bacillus vaginalis type; *f*) the pseudoleucopenic type. The reader is referred to their publication (2) for complete details of this classification.

A more simple classification of the postmenopausal smear was suggested by Salmon and Frank (5) and Geist and Salmon (6); the latter explain the wide variations in degrees of vaginal atrophy on the basis of the varying tempo of the regressive process and continued estrogen elaboration after cessation of menstruation. Geist and Salmon's classification of the various degrees of estrogen deficiency, as determined by morphologic characteristics of smears stained by the fuchsin method, follows.

*Reaction I, advanced estrogen deficiency.* The characteristic features of this type of smear are the complete absence of squamous epithelial cells and the presence of small, round or oval epithelial cells with rather large, darkly-staining nuclei ('atrophy cells'). These are the cells which Papanicolaou and Shorr have described as 'deep cells.' Leucocytes and erythrocytes are present in varying numbers.

In some smears the epithelial cells are few in number and associated with large numbers of leucocytes in others, particularly in very old women, the epithelial cells are very small, few in number and associated with a scattering of leucocytes and erythrocytes.

*Reaction II, moderate degree of estrogen deficiency.* There is a variable number of large epithelial cells, many of which are irregular in shape. The nuclei are relatively large. Interspersed among these cells is a varying number of atrophy cells and leucocytes. The relative proportion of the large epithelial cells to the atrophy cells is variable. What distinguishes this smear from that of *Reaction I* and *III* is the association of the atrophy cells with the larger epithelial cells.

*Reaction III, slight degree of estrogen deficiency.* Prevalence of rather large, irregular epithelial cells is the striking feature of this smear. The cells vary in size and shape, their edges are somewhat irregular and frequently indistinct in outline. They frequently occur in clumps; a few atrophy cells may be present.

*Reaction IV.* The smear consists of large, flat, clearly outlined, squamous epithelial cells with small, deeply-staining nuclei. These cells are larger, more clear-cut, and the nuclei relatively smaller than those in the *Reaction III* type of smear. No atrophy cells and usually no leucocytes are seen.

A simple system of grading these varying degrees of estrogen deficiency on the basis of glycogen content, rather than upon morphology of the cellular elements, was described by Mack and Ale (9) utilizing the iodine-vapor staining technic.

*Grade I.* Complete glycopenia. Smears of this type contain only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris. In extreme grades there is marked paucity of epithelial elements.

*Grade II.* This grade of smear is marked by a greater abundance of epithelial elements than in *Grade I*. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm ('mottled cells'). Diffusely stained brown cells, usually of the small, round variety (deep cells; atrophy cells) may also be present in small numbers. Many glycopenic yellow cells are also found.

*Grade III.* A further increase in cell numbers is evident in this grade as compared to the preceding. The cells are larger and more regular. The diffusely stained cytoplasm has a rich brown color. Non-iodophilic yellow cells are also present in abundance.

*Grade IV.* This grade of smear is easily recognized by the presence, almost exclusively, of large, flat, deeply stained brown iodophilic cells present singly or in large clumps. *Grade IV* represents maximal estrogenic effect and corresponds to the smear of the normal follicular phase.

A somewhat similar scheme, based on proportions of glycogen-containing and glycogen-deficient cells in smears stained by iodine reagents, was proposed by Willson and Goforth (1).

- 1+ only an occasional glycogen-containing cell
- 2+ less than one-third of the cells contain glycogen
- 3+ from one third to two-thirds of the cells contain glycogen
- 4+ more than two-thirds of the cells contain glycogen

**Discussion** As is evident from the foregoing discussion, the variable tempo of regressive changes in the vagina and the persistence of high degrees of estrogen activity from non-ovarian or extrinsic sources produce great variability in the appearance of the postmenopausal vaginal smear, both in its cytology and glycogen content. This has been shown abundantly in smear studies by Papanicolaou and Shorr (2), Salmon and Frank (3); Geist and Salmon (6), Bernstein and Feresten (11), McLaren (12), Mack and Ale (9), and Mack (3). Evidence of postmenopausal estrogen elaboration has also been demonstrated from estrogen titers in the blood and urine of hysterectomized women by Robson and his associates, Frank, Goldberger and Salmon, Schlossberg and Durruty, and by Fluhmann (14).

While Papanicolaou and Shorr have insisted that 'the menopausal type of smear is invariably present after menopause whether or not symptoms exist' it is evident that such smear pictures are not always clearly defined nor readily recognized. Hence, clear-cut evidence of ovarian failure is not invariably demonstrated during the symptom-producing phases of the menopause and the diagnostic value of smears is highly debatable and necessarily limited. Ottaway's conclusion (15) gives a good appraisal.

In spite of promising experimental data, it is obvious from our observations that vaginal smears are far from infallible as clinical objective evidence in estrogenic insufficiency of women. For example, the fact that no estrogenic deficiency is revealed by smears in 4 cases with symptoms which followed castration shows lack of reliability in absolute diagnosis, although the method could well be of some use as corroboratory evidence in vague cases.

#### *Amenorrhea and Other Disorders of the Menstrual Cycle*

Papanicolaou and Shorr also described the vaginal cytology in primary and secondary

amenorrhea. Smear types identical with those they described for the menopause were found.

The *menopausal atrophic type* is characteristic of cases of primary amenorrhea, being associated with an infantile uterus. The deep cells prevail in this type. In secondary amenorrheas, all other types described above are found. The resemblance of the smears in these two conditions (i.e., menopause and amenorrhea), the similarity in their response to the follicular hormone, and the existence of postmenopausal cyclic changes, tend to break down the sharp distinctions generally held to exist between them. From the morphologic standpoint it is frequently hard to classify cases in one group or the other.

In a later publication (16) they describe the vaginal smears in a case of secondary amenorrhea of the stationary or 'fixed' atrophic type. More recently, Papanicolaou spoke of the 'atrophic type of smear, usually found in primary amenorrhea' and a 'crowded type of smear, usually found in primary amenorrhea.' (17).

Moulton (18) has reported the results of the study of vaginal smears in three patients with anorexia nervosa who had disturbances of the menstrual cycle. In one instance, smears of the follicular type with irregular cyclic changes were interpreted as

evidence of moderate continuous estrogen activity, as the cells were of the intermediate type rather than of the basal type, and were distinct, well formed, and partly cornified. The percentage of cornification was taken as the best and only quantitative measure of the level of estrogen activity, and cyclic increases in this were found to coincide with, or just precede vomiting attacks. The quiescent level of cornification between attacks was 2 to 10 per cent, with definite increase during attacks to 25 to 40 per cent. They were thought to be of significant magnitude because they consisted of at least 20 per cent increase in cornification, while the margin of error in estimating each smear was about 5 per cent as shown by rechecking. Smears were also taken three times a week on case 3 for five months, but no cyclic changes were found, the smears being of the atrophic type, described as being typical of primary amenorrhea and severe secondary amenorrheas. Vaginal smears were useful in this study for research rather than for therapy.

Ripley and Papanicolaou (17) also reported study of vaginal smears in menstrual disorders in 31 women with schizophrenia, depression and elation. Their investigations showed 'well expressed follicular reactions' in the presence of normal cycles, whereas retarded menstruation was attended by the 'relatively frequent occurrence' of a delay in the appearance of follicular phase. In most patients, with normally long intervals, the follicular phase in smears was either poor or absent. Such atypical follicular

as ones in which 'cornified cells of the follicular type are intermixed with smaller, round or oval deep cells, indicative of a subnormal estrogenic secretion.' Short cycles were rarely observed in this study, although in one instance of a 19-day interval the smear was marked by the persistence of numerous cornified cells during the premenstrual period, whereas in the normal premenstrual stage their numbers decrease gradually. Scant menstrual bleeding was observed in instances in which 'the follicular reaction was poorly expressed' and the interval was lengthened.

*Discussion.* While the value of the vaginal smear method in clinical research of cyclic disturbances has been shown in the examples cited above, there is little evidence at present to indicate its usefulness in gynecologic practice. Readily distinguishable vaginal atrophy indicative of extensive ovarian deficiency appears to be characteristic of certain types of primary amenorrhea; the highly variable pictures seen in the vaginal smears of cases of secondary amenorrheas and of irregularities of the menstrual interval make this procedure of questionable value. Campbell and Sevringhaus (19) claim practical importance of vaginal smears, along with endometrial biopsy and pregnandiol determinations, for accurate diagnosis and management of amenorrhea. The lack of other confirmatory reports from clinical workers would appear to indicate the limited value of the smear method in this field.

### *Failure of Ovulation*

Papanicolaou's description of the 'ovulative smear' suggested the use of this method for the detection of ovulation or the recognition of anovulatory cycles in investigations of functional sterility. The ovulative stage which follows upon the leucopenic follicular phase is recognized, according to Papanicolaou, by the sudden appearance of leucocytes and a few erythrocytes. After accomplished ovulation, there follows the luteal phase of the cycle the smear for which is described as consisting of cells which are folded, clumped, fragmented, and associated with many leucocytes; prior to ovulation, the cells are intact, discrete, largely cornified and unaccompanied by leucocytes.

Use of the smear method for the detection of ovulation or ovulatory failure has been advocated chiefly by Rubenstein (20, 21) who combines the cytologic changes described above with determinations of basal rectal temperature for this purpose. Depending upon evidence of a sudden rise of basal rectal temperature and the ovulatory changes in vaginal smears, Rubenstein reported a high incidence of anovulatory menstruation in cases of sterility. He pointed out that the presence of infection or chronic irritation may, however, invalidate the interpretation of both smears and temperature readings. Zuck and Duncan had previously relied upon a rise both in vaginal pH and rectal temperature to postulate the occurrence of ovulation (22).

In a recent critical study of the smear method for detecting ovulation, Krohn, Harri and Hechter (23) indicate that numerous factors complicate the evaluation of ovarian function by this means. They showed that *a*) artifact peaks of desquamation frequently occur without a corresponding drop in cornification and these do not signify ovulation, and *b*), persistently high levels of estrogen may induce desquamation similar to that produced by progesterone during the luteal phase of the cycle. They believe, however, that proper interpretation of daily vaginal smears will 'in most cases' indicate whether or not the patient has ovulated, although no explanation for 'artifact desquamations' is offered. They supplement observations on luteal activity by vaginal smear studies with determinations of urinary pregnandiol.

No confirmatory evidence of the value of vaginal smears for the detection of ovulation has as yet been produced.

### *Senile Atrophic Vaginitis*

The use of vaginal smears for the recognition of postmenopausal vaginitis resulting from estrogen deficiency and the control of specific therapy of this condition was reported by Ottaway (15). The limited value of smears for this purpose is summarized in his conclusion: 'In the diagnosis of senile vaginitis the examination of vaginal smears could be of considerable value in ruling out the suspected but not true cases.'

# VAGINAL SMEARS FOR EVALUATION OF THERAPY

The striking and easily demonstrated transformation of the atrophic vaginal smear by the administration of estrogens and the definite induction of atrophic changes in the normal and estrogen-stimulated mucosa by androgens suggested the usefulness of the smear method as a means for evaluating the success of therapy using the sex steroids.

*Estrogen therapy.* Papanicolaou and Shorr (2) were the first to advocate the use of vaginal smears for objective determinations of the effectiveness of estrogen therapy independent of symptomatic response. They suggested the attainment of the follicular phase as the therapeutic goal.

The fact that symptomatic relief may occur before the vaginal smear change raises the question whether the optimum state is reached when symptoms are relieved or when the follicular phase is induced. Analogies are numerous with other efficiency states, in which objective as well as subjective criteria are available. The relief of the symptoms of myxedema at lower than normal basal metabolic levels, and the abolition of tetany, with the blood calcium and phosphorus still far from normal, are examples. Such partial changes are welcome from the standpoint of the patient's comfort. But it is generally recognized that they are less desirable than the complete restoration of the physiologic state prevailing with the normal function of the hormones involved. It is for this reason as well as the other considerations mentioned above, that we are inclined to consider the induction of the follicular phase as the more reliable standard in the treatment of the menopause syndrome.

Papanicolaou and Shorr further utilized the attainment of the follicular phase as a therapeutic test to distinguish between menopausal and pseudo-menopausal symptoms, since the latter will persist after complete smear changes are obtained.

Acceptance of the vaginal smear method as an important or necessary adjunct to the evaluation of estrogen therapy has been recorded by several investigators. Campbell and Sevringhaus (19) consider smears, along with endometrial biopsies and pregnandiol determinations, essential for accuracy in diagnosis and appraisal of therapy. Smith (24), using smears as diagnostic measures and as guides to therapy found that 'alterations in the smear practically always parallel symptomatic improvement.' Schneider (25) states that 'vaginal smears provide an efficient and accurate index to physiologic action of estrogen and although of value in the individual case are not essential rou-

tinely.' Ottaway (15) recognized the occasional usefulness of smears in the treatment of senile vaginitis as 'a means of gauging the dosage of estrogenic substance to attain the normal type IV smear necessary for cure.' Simpson and Mason (26) employed vaginal smears to demonstrate the effectiveness of vitamin A therapy in senile vaginitis which they attribute to deficiency of vitamin A as well as of ovarian hormones.

Other investigators have been less enthusiastic and even critical of the value of vaginal smears in therapeutic appraisals. Werner and his associates (27) wrote:

It is quite evident from the present study that changes in the vaginal secretion are a much less delicate index of the effectiveness of estrogenic material than is an examination of the uterine mucosa secured by curettage. It is also quite obvious that symptomatic relief can be secured in dosages that are too small to produce definite changes in the vaginal secretion, since the group of subjects receiving the smallest dosage apparently secured as much relief of symptoms as those who received larger doses. In view of these facts we feel that the question may legitimately be raised whether the objective of theelin medication in castrate and menopausal cases should be pushed to the point of full follicular phase of the menstrual cycle, as suggested by Papanicolaou.

Ottaway concluded (15):

In spite of promising experimental data, it is obvious from our observations that vaginal smears are far from infallible as clinical objective evidence in estrogenic insufficiency of women. For example, the fact that no estrogenic deficiency was revealed by smears in 4 cases with symptoms which followed castration shows lack of reliability in absolute diagnosis, although the method could well be of some use as confirmatory evidence in vague cases. In treatment of the so-called menopausal syndrome, progression of smears toward an estrogenic sufficiency type, showed a general relationship to improvement in symptoms, but with so many exceptions as to be of only slight value in determining dosage for relief.

The same viewpoint was expressed by Bennett and TeLinde (28) who state:

We do not feel that it is necessary for the practitioner who is treating menopausal symptoms to follow the menopausal smears. In fact, to be guided entirely by the smears would in some instances be misleading.

*Androgen therapy in women.* Vaginal smear studies by Papanicolaou, Shorr, and Ripley (29), as well as those of other investigators, have demonstrated atrophic changes following the administration of testosterone propionate. While these reports suggest the usefulness of vaginal smears as an index of the effect of androgens upon women, no clinical application of this method has as yet been made in the management of gynecologic disorders with male hormone preparations.

## VAGINAL SMEARS FOR HORMONE ASSAYS

Confirmation of the observations that the atrophic vaginal smear can be readily transformed into one resembling the follicular phase of the normal cycle has resulted in numerous attempts to evaluate the effectiveness of various hormone preparations in human subjects by this method. The hormones tested by this means now include, not only the various natural and synthetic estrogens, but also progesterone, androgens and gonadotropins. Only a few of the more representative articles of the voluminous literature are cited in this appraisal of the vaginal smear method.

*Estrogens.* Potency of the various products has been judged by their ability to transform the atrophic vaginal smear of menopausal or castrated subjects into one characteristic for the cytologically normal follicular phase. This evidence of estrogenic efficiency has been shown for estrone,  $\alpha$ -estradiol benzoate,  $\alpha$ -estradiol dipropionate, ethinyl estradiol and diethylstilbestrol. The effectiveness of these preparations has been shown also by oral, parenteral, sublingual, vaginal routes of administration and by subcutaneous implantation and inunction. The cytologic criteria of Papanicolaou and Shorr were made the basis of most determinations. The glycogen index was employed by Mack (8), Mack and Ale (9) in studies of oral, vaginal and parenteral administrations of estrone. Willson and Goforth (10) tested diethylstilbestrol by this method and observed that an increase in vaginal glycogen after treatment could be observed before changes in cell type were detectable. Herrnberger and Horstmann (30) have assayed estradiol benzoate by means of the glycogen index of smears stained by the complicated Best's carmine method. Their studies were made upon young children. Further investigations are necessary to determine whether the technically simple glycogen methods or the more complex procedures based upon cytologic criteria are best suited for estrogen assays in the human subject.

Stoddard and Metzger (31) have employed the vaginal smear method to determine the comparative potencies in women of orally administered diethylstilbestrol, and  $\alpha$ -estradiol benzoate and estrone by intramuscular injection.

The effectiveness of these substances was compared by determining the minimum amount of each which was necessary to produce a mid-interval type of smear response in the middle 75 per cent of each group of menopausal subjects on the day following cessation of a 10-day period of treatment. When assayed by this procedure (which follows closely the manner of assay of estrogens in laboratory animals) they determined that 1.0 mg. of estrone (intramuscularly), 0.42 mg. of  $\alpha$ -estradiol benzoate (intramuscularly) and 0.5 mg. of diethylstilbestrol (orally) are comparable dosages in the human subject. Ferin (32) proposed a similar approach to determine human units for estrone, estradiol and stilbestrol from vaginal smear and endometrial responses in castrated women. Mack and Ale (9) have compared the efficiency of orally and parenterally administered estrone on the basis of glycogen responses to equal weighed amounts given to menopausal subjects having advanced vaginal atrophy. Further large scale investigations on human subjects are necessary to determine whether this method will provide reliable data for clinical use. The widely divergent results of animal assays indicate the need for a trustworthy means of determining human responses and requirements. The published reports of estrogen determinations based upon vaginal smear responses in human subjects indicate a promising approach toward fulfillment of this need.

*Progesterone.* The effect of progesterone on vaginal smears was studied by Shorr (33). His report indicates that the administration of progesterone and estrogen reproduces, more fully than estrogen alone, the physiologic picture of the second half of the menstrual cycle described by Papanicolaou. No other study of this type appears in the available literature. Hartman and Speert's study (34) on unprimed castrated rhesus monkeys indicates that growth and cornification of the vaginal mucosa results after progesterone administration and suggests that there is little difference in the vaginal action of estrin and progesterone.

*Gonadotropins.* Shorr and Papanicolaou (16) and Campbell and Sevringhaus (19) appear to be the only investigators who have attempted to judge the efficacy of gonadotropic hormone preparations by evidence from vaginal smears.

of increased levels of estrogenic response Shorr's patient showed typical estrogenic smear changes after the first course of therapy with gonadotropic hormone which resulted in menstruation; the patient, thereafter, remained refractory to further treatment as was shown by continued 'fixed' atrophic smears. Campbell and Sevringhaus consider gonadotropic hormone therapy useless if vaginal smear changes (as well as endometrial patterns and pregnandiol determinations) do not indicate that full ovarian activity has been attained.

**Androgens** The anti-estrogenic action of androgens has been demonstrated in vaginal smears by the production of atrophy in the normal and estrogen-stimulated mucosa of women. Salmon, Walter and Geist (7) have also shown that testosterone brings about a disappearance of glycogen from the cells of the vaginal epithelium. The use of the vaginal smear method for evaluating androgen preparations was suggested by Shorr, Papanicolaou and Ripley (35).

Testosterone propionate inhibited the menstrual cycle of a young menstruating woman. Menstruation was resumed spontaneously 28 days after cessation of therapy. Lysination of the vaginal smears was made during the various phases of the menstrual cycle. With the administration of the male hormone, a transition to an atrophic menopausal type of smear took place. With the cessation of therapy the smears returned to normal. These definite changes in the vaginal secretion offer a simple and reliable method for evaluating the effect of the male hormone in women.

This has been abundantly confirmed in trials of testosterone propionate by Rothermich (37), Geist, Salmon, Gaines and Walter (38), Rothermich, Postle and Foltz (39), and others. In an early publication in 1937 Salmon (40) reported a contrary observation in a 46-year-old castrate after injection of 400 mg. of testosterone propionate.

It would appear from this study that testosterone propionate when given in adequate dosage can inhibit the gonadotropic hyperactivity of the hypophysis in the female castrate and also produce a full estrogenic effect on the vaginal mucous membrane in a female castrate—thus paralleling two phases of biologic activity of the estrogenic substances.

This report appears to be the only one to contradict the antigynecogenic action of testosterone upon the human vagina.

Gaines, Geist and Salmon (41) noted no suppressive action upon the vaginal mucosa from the administration of various dosages of preg-

nemolene and concluded, thereby, that its androgenic effect was *nil* or negligible.

#### CONCLUSIONS

The vaginal smear method has yielded a wealth of scientific information concerning the endocrine physiology of the menstrual cycle. In scientific investigations of the menopause and other conditions of ovarian failure, smears have also provided valuable objective evidence of functional derangement. As a method of diagnosis of ovarian dysfunction or failure in clinical practice the vaginal smear method has very limited usefulness because of: a) difficulties of interpreting the bizarre and highly variable histologic smear patterns, and b) the frequency of normal smears in the presence of signs and symptoms of ovarian failure.

As a clinical method of determining the effectiveness of estrogen therapy, the vaginal smear technic may provide objective evidence of therapeutic results in limited instances in which vaginal atrophy accompanies other signs or symptoms of ovarian failure.

The most promising field of usefulness of the vaginal smear method is its application as a means of estrogen and androgen assay in the human female.

Until the technic of preparation and the criteria of interpretation of vaginal smears are simplified, use of the procedure will be restricted to research studies.

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# COMMUNICATION TO EDITOR

## A NEW METHOD FOR STAINING SPERMATOZOA

IT is only during the past 20 years that clinicians interested in the study of male infertility have realized the importance of investigating the physiology and morphology of spermatozoa. Previously the presence of live spermatozoa was accepted as conclusive evidence of male fertility. Many workers are now stressing the importance, not only of numbers, motility, biochemistry and endurance, but also of morphology. Moench<sup>1</sup> was the first to apply statistical methods to the study of the morphology of human semen as related to sterility. He found that in specimens from normally fertile human males the number of abnormal head forms never exceeded 20 per cent of the total count. As values very close to this have been obtained by almost all of the many later workers<sup>2,3,4</sup> a ratio of 20 per cent abnormal forms has become more or less accepted as the region of demarcation between normal and lowered fertility.

The range of abnormalities in sperm is very wide and includes malformations of head, neck and tail, those of the head being most important and numerous. For this reason, various methods have been devised to stain differentially the head, neck and tail. In most cases the procedure is time-consuming and involves so many steps that each slide must be handled individually. In view of these disadvantages, our object was to find a differential stain which could be used successfully even by the inexperienced, and which would require a minimum of time and effort. We believe that this has been achieved.

The stain, a modification of the Pappenheim-Saathoff formula<sup>5</sup> has been used for smears of

gonococci,<sup>6</sup> but to our knowledge has never been recommended for the staining of sperm. With its use as outlined below the sperm head is colored blue-green, the acrosome lighter than the posterior part of the head; neck and tail are pink to lavender, less distinct than the head but clearly visible. We believe there may be a tendency for abnormal forms to stain more darkly than the normal.

### FORMULA AND PREPARATION

methyl green, dye content 60%	1.0 gm.
pyronine, bluish, certified	0.2 gm.
methyl alcohol, absolute	100.0 cc.
phenol, 2% aqueous solution	100.0 cc.
glycerol, c.p.	20.0 cc.

Dissolve the dyes in the alcohol and phenol by intermittent shaking about 2 hours each day for 2 days, using a mechanical shaker. Filter and add the glycerin. Refilter into dropping bottle as the supply is needed.

An alternate formula follows:

methyl green, dye content 60%	1.0 gm.
pyronine, bluish, certified	0.25 gm.
alcohol, 95%	5.0 cc.
glycerol, c.p.	20.0 cc.
phenol, 2% aqueous solution	100.0 cc.

Heat solvents to about 60° C. Rub dyes together and add to solvents. Agitate until dyes are dissolved. The solution should be allowed to stand for an hour or more before filtering.

### PROCEDURE

1. Prepare a smear on a clean dry slide. Dry in air.
2. Fix in a solution of 1 part 95 per cent alcohol, 1 part ether, and dry in air; or fix by heat.
3. Flood the slide with stain. If desired, heat the slide until steam rises from the stain. This latter step is not necessary but results in better staining of some cellular elements. Let stand 5 minutes.
4. Wash with tap water.
5. Dry and examine with oil immersion lens.

<sup>6</sup> WALTON, S. T.: Quick and reliable method for staining gonococcus smears. *J. Lab. & Clin. Med.* 24: 1308 1939.

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<sup>1</sup> MOENCH, G. L.: Sperm morphology in relation to fertility. *Am. J. Obst. & Gynec.*, 22: 199, 1931.

<sup>2</sup> HOTCHKISS, R. S., E. L. BRUNNER AND P. GRENNLEY: Semen analyses of two hundred fertile men. *Am. J. M. Sc.*, 196: 362 1938.

<sup>3</sup> STIASNY, H.: Method of examination of sperm of fertile and sterile males with special reference to morphology of spermatozoa. *Zentralbl. f. Gynäk.* 61: 2051, 1937.

<sup>4</sup> POLLAK, O. J., AND C. A. JOEL: Sperm examination according to the present state of research. *J. Am. Med. Assoc.* 133: 395 1939.

<sup>5</sup> CONN, H. J. Biological stains. Commission on standardization of biological stains. Geneva, 1929.

This method has been used in semen studies of over 350 cases, chiefly cases from private practice and the results have been similar to those obtained with other-more complicated differential stains.

has been used in the study of over 350 cases of suspected low fertility in the male.

#### SUMMARY

Formula and procedure are given for a simple rapid differential stain for human spermatozoa. Staining results are briefly described. The method

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## HORMONE THERAPY AND BENIGN HYPERTROPHY OF THE PROSTATE

THE POSSIBILITY of endocrine therapy for benign hypertrophy of the prostate is of considerable interest to the physician. Reports of successful treatment of this condition have appeared, and the doctor is urged to try an estrogen or an androgen, frequently by the patient himself, more often by the ubiquitous detail man.

It may be well to examine, for the benefit of the practicing physician, some of the experimental evidence which led to attempts at endocrine therapy for nodular prostatic hypertrophy.

The response of the prostate to many varieties and combinations of hormones has been investigated in many animals. In rodents, gonadotropic hormones given to intact animals or androgens administered to immature or castrated animals causes growth of both parenchyma and stroma of the compound prostate gland. Estrogens affect mainly the utricle, and with prolonged treatment cause a squamous cell metaplasia, not only in the utricle but also in the collecting ducts of the prostatic acini.

The dog is particularly interesting in that a high incidence of cystic glandular hyperplasia of the prostate occurs spontaneously with ageing. Although there is a great increase in mass of the prostate in such aged dogs, there is no formation of fibromuscular nodules, and so far as appears in the records, little or no urinary retention.

In dogs reported by de Jongh and Kok,<sup>1</sup> estrogen caused a cystic dilatation of prostatic glands and the utriculus with squamous metaplasia and desquamation. There may have been some suggestion of fibromuscular overgrowth but in no instance has this been localized or nodular. Huggins<sup>2</sup> and his associates demonstrated prostatic enlargement in the dog after estrogen treatment. The gland was markedly enlarged, but with cystic dilatation of the prostatic acini

only, and without fibrosis, nodule formation or urinary retention.

Benign prostatic hypertrophy has not been reported for any species of monkey or any sub-human primate. In a report of an old rhesus monkey with a well developed adenocarcinoma of the prostate, there was no evidence of concurrent benign prostatic hypertrophy.

Young preadolescent castrated male monkeys have been treated with estrone, with testosterone propionate and with combinations of the two for brief periods.

In Zuckerman's series<sup>3</sup> two monkeys were treated with small doses (10  $\mu$ g and 100  $\mu$ g, respectively) of estrone for a year. In these two, the main effects of the estrone consisted in an increase in size of the fibromuscular stroma of that portion of the prostate which forms the bed of the utriculus.

The monkeys which have been treated were young animals. It is possible that further developments would be observed if old animals were used. Fibromyxomatous nodular hyperplasia of the human prostate is structurally very similar to fibromyomata of the uterus. Lesions similar to those of the human uterus have been induced in guinea pigs by prolonged estrogen stimulation. No observable lesion has yet been induced in the fibromuscular tissue of the uterus of the rhesus monkey. Treatment of fully mature female monkeys with an estrogen for periods as long as 170 days, produced no such change. Aged monkeys, which had received estradiol crystals or pellets with a total dosage of 825 mg during 24 months, have likewise shown no fibromyxomatous nodules in the uterine musculature.<sup>4</sup>

The possible endocrine participation in benign prostatic hypertrophy has, as yet, received no support from animal experimentation. The prostate may be induced to grow greatly in size, and cystic dilatation of the glands may occur, but

<sup>1</sup> DE JONGH, S. E., AND D. J. KOK. *Acta Urol. Neerland* 177: 1935. Microphotographs of the work of these investigators was published in ZUCKERMAN, S. AND GROOME, J. R. *J. Path. & Bact.* 44: 113, 1937.

<sup>2</sup> HUGGINS, C. Exhibit, Annual Meeting American Medical Association, New York City, 1940.

<sup>3</sup> ZUCKERMAN, S. Effects of prolonged estrogenic stimulation on the prostate of the rhesus monkey. *J. Anat.* 72: 264, 1938.

<sup>4</sup> ENGLE, E. F., AND C. KRAVOWER. Unpublished.

no fibromuscular lesions have been produced in the male, and urinary retention as a result of such treatment has not been induced.

The excretion of known gonadotropins or steroids by patients with benign prostatic hypertrophy does not differ significantly from that by other patients of similar ages.

The well-known relationship of the testes and their steroids to the growth and maturation of the human prostate, and the suggestive relationship in senile involution of the prostate, make it inadvisable, however, even in the face of negative data to imply that endocrine changes may not be at least a factor in benign nodular hyperplasia. Several papers<sup>5</sup> have been presented showing clinical effects or improvement of patients with this disorder, after treatment with certain steroid hormones.

These papers with their case histories are difficult to evaluate. The patient calls on the physician not because of prostatic hypertrophy, but because of urinary frequency, painful micturition or acute retention. Many manipulative procedures give temporary relief. Prostatism itself may be intermittent, with spontaneous remissions of the disease. Any claims for relief of prostatism, other than surgical, must be scrutinized carefully in the light of the well known 'control series' of patients who refused operation for obstructive prostatism. This notable group reported by Clarke<sup>6</sup> were patients who were observed after refusal of operation for about four years, and in whom some degree of urinary efficiency was maintained by routine procedures. These cases are not reviewed to contrast the de-

gree of satisfaction obtained in surgical as compared with non-operated cases, but should be against undue optimism regarding 'cures' of prostatism by endocrine therapy.

There may be theoretical grounds for belief that either estrogen or androgen might be effective therapy in prostatism. The difficulties evaluating the results of such therapy in terms other than 'patient relief' are very great. Tangible evidence of structural improvement is meager or lacking and it is doubtful that remissions or relief of this type of prostatism by endocrine therapy is any greater than has been obtained by other procedures short of surgery.

The brilliant demonstration by Huggins<sup>7</sup> that castration results in physiologic and clinical improvement of patients suffering from adenocarcinoma of the prostate indicates clearly, however, that the door is not closed to further research on the hormonal relations of prostatic physiology and pathology.

Work reported to date has not shown clearly an endocrine rôle in the etiology or the successful therapy of nodular hyperplasia of the prostate.

New interest and activity in investigating the rôle of the liver and the adrenal in the intermediary metabolism of the steroids, and the possible relations of various steroids to problems of collagen formation and fibrosis, all promise to make problems of the pathology of the prostate not be neglected.

For the time being, however, the patient suffering from urinary retention as a result of nodular hyperplasia of the prostate will be afforded greater relief by the surgeon than by the endocrinologist.

E.T.E.

<sup>5</sup> LOWER, W. E., F. C. SCHLUMBERGER AND E. E. FERGUSON: The hormonal treatment of benign enlargement of the prostate. *Surg., Gynec. & Obst.* 71: 354. 1940.

<sup>6</sup> CLARKE, R.: The prostate and the endocrines. *Brit. J. Urol.* 9: 254. 1937.

<sup>7</sup> HUGGINS, C., AND C. V. HODGES: *Cancer Res.* 1: 2 1941.

## ADRENAL-CORTEX EXTRACT AND SHOCK

THE GENERAL picture of functional depression following destruction of the adrenal cortex and that of surgical shock are suggestively similar—a fact that has long been recognized. Many writers have speculated as to the degree to which the manifestations of shock might actually mirror cortical failure. Claims have been made that cortical extract when administered to patients or animals in shock to some extent parallels its brilliant efficacy in counteracting adrenal deficiency. On the other

hand, many essentially negative results have been obtained and doubt is growing as to the practical value of adrenal-cortex therapy in the treatment of shock.

Among those who have reported favorable results are workers in the laboratories of the Michael Reese Hospital in Chicago. Here a method was developed for the production of shock by occlusion of the veins in the hind legs of dogs. It was found that this procedure resulted in shock followed by death, usually within a few

ious in 87 per cent of the subjects. Desoxy corticosterone acetate was found to have considerable protective value. More recently Shleser and Asher<sup>1</sup> of the same institution have repeated the work, using, instead of the synthetic preparation, a commercial extract of adrenal-cortex material. It seemed reasonable to hope that its other active components might add to the efficacy of the contained desoxy corticosterone since previous investigators had found that cortin was effective in preventing the occurrence of histamine shock in adrenalectomized animals, it also had a beneficial effect on the reduced blood pressure and the plasma-fluid loss in dogs which had received, intravenously, extracts made from obstructed loops of intestine. More immediately relevant are earlier findings that cortical extract had an ameliorative effect on shock following intestinal trauma in rats, and in the prevention of traumatic shock in dogs.

In Shleser and Asher's new work the veins of one limb of the dog were ligated aseptically. Suspensions of sterile lamp black in normal saline solution were then injected. As criteria of the development of shock, measurements of blood pressure, heart rate, relative blood cell-volume (hematocrit) and limb circumference were recorded at regular intervals postoperatively. To the experimental animals adrenal cortical extract was administered subcutaneously in dosage varying from 17.5 to 39.0 cc—the average being 23.3 cc. One-half of the total dose was given as a prophylactic 12 hours preceding the operation and the remainder in divided doses over the first 12 hours, following the operation.

Twelve experimental animals were used. Five of these died within 24 hours after the operation and postmortem studies supported the assumption that the deaths had been due to shock. One dog, in addition, died of pneumonia within the first day but appeared not to have developed shock. Thus 50 per cent of the animals survived, as compared with only 13 per cent which, on the basis of previous experiences, was expected.

In the 5 animals which succumbed to shock the affected limb had increased in size about one-third beyond that of its control member. This increased weight amounted to from 3 to 8 per

cent of the total body weight and thus represented a loss of plasma fluid equivalent to from a half to three-fourths that of the total blood volume. The treatment with adrenal cortical extract seemed to have been completely ineffective in these 5 animals since they survived no longer than did untreated controls. Among the 6 dogs that survived limb enlargement was slightly less, but occurred after a longer interval than in those that died. In 3 of the 6, transitory fall of blood pressure was noted but in the other 3 such did not occur. Slight hemoconcentration occurred in 3 and no significant change in the other 3 dogs. Among the 6 survivors none showed clinical signs of developing shock.

To what extent the induction of limb-edema induces conditions of true 'shock' may be questioned. The nervous system is obviously spared the bombardment of nociceptive impulses that result from ordinary types of bodily injury. Furthermore, the experimental procedure fails to reproduce the psychic elements that seem to contribute importantly to the development of surgical shock in man. Even so, however, the new work is suggestive and offers encouragement for further investigations. It is quite possible, as the authors suggest, that with greater knowledge of the composition of the adrenal extract and further research on the physiology of its active components still more satisfactory results can be achieved.

Among the questions upon which further evidence is needed is whether adrenal cortical hormone may be effective when given after shock has supervened or whether its effectiveness is limited to instances in which it is used, as in Shleser and Asher's work, prophylactically as well.

Another aspect of the problem is the question as to the optimal number of doses into which the given amount of extract should be divided. It is perhaps relevant that Swingle and co-workers<sup>2</sup> have found that a given amount of plasma used in the treatment of constriction shock was much more effective when given in 5 divided doses than when administered as a single infusion.

R G H

<sup>1</sup> SHLESER, I. H., AND R. ASHER. Efficacy of adrenal cortical extract and of pargoline in the prevention of experimental shock following venous occlusion of a limb. *Am J Physiol* 138 1 1942.

<sup>2</sup> SWINGLE, W. W., J. W. REMINGTON, W. KLEINBERG, V. A. DRILL AND W. J. EVERSOLE. An experimental study of the tourniquet as a method for inducing circulatory failure in the dog. *Am J Physiol* 138 156 1942.



# LETTERS

## USE OF PITRESSIN TANNATE IN OIL AS A HEMOSTATIC AGENT IN MENORRHAGIA AND METRORRHAGIA

TO THE EDITOR:

The use of pitressin tannate in oil as a hemostatic agent in a series of cases of menorrhagia and metrorrhagia has been attended with uniformly good and rapid results. This use of a standard product appears to be new.

Pitressin tannate in oil is a water-insoluble preparation of the pressor and antidiuretic principle of the posterior lobe of the pituitary gland suspended in oil.\* Injection of this intramuscularly is followed by slow absorption and prolonged action. It was originally produced for use in diabetes insipidus and has been used successfully in this condition.<sup>1 2 3</sup> Because of its prolonged vasoconstricting effect its use in menorrhagia and metrorrhagia or functional uterine bleeding seems logical.

The 10 patients treated included 4 with menometrorrhagia and 6 with metrorrhagia of the premenopausal and menopausal type. Without exception they responded with cessation of the flow within 6 to 72 hours following administration of the first or second dose of 1 cc. in oil, given intramuscularly.

Two of the 4 cases of menometrorrhagia were young girls. One had bled for 2 months and the other for 28 days. In each case two injections of the pitressin tannate in oil were sufficient to control the bleeding. In these cases of prolonged bleeding it has been found that two injections of 1 cc. each, given at 3-day intervals a few days before the next period is due, will prevent the menorrhagia.

When the periods are irregular, difficulty will naturally be encountered in estimating the date the next menstruation is due; but in these 4 cases of menometrorrhagia, the injections were begun approximately 20 days after the beginning of the last flow, except in the one case which flowed 2 months. In this individual the injections were given 2 weeks after the flow had been stopped by the administration of pitressin tannate in oil.

In 6 cases of premenopausal and menopausal metrorrhagia, one or two injections of 1 cc. of the pitressin tannate in oil controlled the bleeding. These cases had been classified as functional uterine bleed-

ing. Naturally as in all cases of this type the usual precautions should be taken to rule out organic causes of bleeding. Metrorrhagia due to carcinoma may be temporarily checked by treatment and thus give a false sense of security.

No other form of therapy that I have used for functional uterine bleeding has given such a prompt response. This treatment is also economical, which certainly is in its favor since so much endocrine treatment is expensive.

No untoward results other than a mild headache have been observed. Occasionally stinging and burning at the site of injection were complained of.

There is, of course, the possibility of excessive water retention if the material is given in high dosage or over prolonged periods. The signs and symptoms of excessive water retention are rapid weight increase, headache, listlessness and drowsiness. The dosage should be reduced or treatment suspended in such instances.

So far I have used only the 1-cc. dose, and it is quite possible that smaller doses than this will suffice. However, so few injections have been necessary in the patients thus far observed that there has seemed to be no danger of overdosage. Naturally, good judgment should be used in patients with hypertension, nephritis, and cardiovascular disease.

Greenblatt<sup>5</sup> concludes that the myometrium as well as its vascular supply is of great importance in metrorrhagia. He says that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict or be constricted following the initial extravasation of blood distally. The endometrium seemingly plays a minimal rôle in this type of bleeding. If this is true then the prolonged vasoconstricting effect of pitressin tannate on the myometrial vascular system would help to explain its benefits in menometrorrhagia. Control of the bleeding tends to prevent the secondary anemia which so frequently accompanies these conditions.

This report is made only to stress the fact of the prompt control of functional uterine bleeding. Further studies are, of course, necessary. The use of pitressin tannate in oil in other conditions in which prolonged uterine vasoconstriction is desirable suggests itself.

As a preventive of functional uterine bleeding in subsequent periods, the practice of giving the drug a few days before onset of the expected flow seems to warrant further study. So far, in the few cases tried, it

<sup>5</sup> GREENBLATT, R. B.: *J. Clinical Endocrinology* 2: 642, 1942.

\* Parke, Davis & Company.

<sup>1</sup> GREENE, J. A., AND L. E. JANUARY: *Proc. Soc. Exper. Biol. & Med.* 44: 217. 1940.

<sup>2</sup> STEPHENS, D. J.: *Proc. Soc. Exper. Biol. & Med.* 44: 240. 1940.

<sup>3</sup> THORN, G. W., AND K. E. STEIN: *J. Clinical Endocrinology* 1: 680. 1941.

<sup>4</sup> CADY, L. D.: *J. Missouri M. A.* 39: 19. 1942.

has been successful in preventing excessive flow, the periods usually lasting 4 to 6 days with a moderate amount of bleeding.

Further studies are being made and I hope this report will prompt the use of the drug by others so that

its value in functional uterine bleeding will be adequately determined.

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Detroit, Michigan

## PSYCHOSOMATICS OF MATERNAL BEHAVIOR

TO THE EDITOR

In a recently published article<sup>1</sup> I reported some of the results of a search for constitutional factors in maternal behavior. Interviews were held with 72 women nearly all of whom were mothers of children who were treated for various behavior problems. A relationship was found between the habitual number of days of menstrual flow and the strength of the maternal feeling. Thus a significantly higher proportion of strong maternal impulses appeared in the woman having a flow of 6 to 8 days than in the group flowing from 2 to 4 days.

The findings have withstood the test of rigorous

<sup>1</sup>LEVIN D M Psychosomatic studies on some aspects of maternal behavior *Psychosomatic Medicine* 4: 223 1940

statistical analysis and have been confirmed in more recent studies. Aside from the work of Wiesner and Sheard<sup>2</sup> and more recently that of Riddle and his collaborators<sup>3</sup> on the influence of prolactin on maternal behavior, I know of no data from the field of endocrinology which seem to throw light on the relationship. If your readers can offer further relevant data or explanation regarding the matter I shall be glad to receive the same.

DAVID M LEVIN

136 East Fifty-seventh St  
New York City

<sup>2</sup>WIESNER P B AND N M SHEARD Maternal Behavior in the Rat. Oliver and Boyd, London 1935

<sup>3</sup>RIDDLE O Lactogenic factor of the pituitary *J Am Med Assoc* 104: 636 1935

## CREATINE METABOLISM AND METHYL TESTOSTERONE

TO THE EDITOR

I read with great interest the splendid article, Influence of Methyl Testosterone on Muscular Work and Creatine Metabolism in Normal Young Men in the November issue of the *JOURNAL OF CLINICAL ENDOCRINOLOGY*.<sup>1</sup>

CREATINE EXCRETION PER 24 HOURS IN HYPOGONAD MALES RECEIVING METHYL TESTOSTERONE

Case	Initial Values	Treatment with Methyl Testosterone					
		40 mg or more daily				20 mg daily	
	mg	mg	mg	mg	mg	mg	mg
P H	225	740	540			217	173
G R	50	400	460	750	840	125	100
J H	164 36	329	360			169	
R T	38	510	440			120	
R C	0	266	300			80	110

I wish to report to you that similar findings were observed in our hypogonad cases (see table). We explained this phenomenon in terms of the recent works by Beard<sup>2</sup> on the effect of methylating substances on creatinuria. In view of this I believe that it may be suggested that large doses of methyl testosterone (40 mg or more) act as methylating substances and that evidence of increased creatinuria probably represents a pharmacologic effect of an over dose. You will note from our table that when dosage was lowered to a level of 20 mg (quite sufficient for the desired physiologic effects) this excessive creatinuria disappeared.

B N FAGER, M D

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<sup>1</sup>SMITH L T, A T HENSCHILL AND A KEYS *J Clin Endocrinology* 2: 649 1942

<sup>2</sup>BEARD H H Annual Review of Biochemistry Stanford Univ. Press 1941





# Abstracts of

## CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLÉN, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, PATRICIA H. SMITH, EMMERICH VON HAAM, HAROLD WOOSTER.

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### BOOK REVIEWS

CORNER, GEORGE W.

The hormones in human reproduction. Princeton University Press: Princeton, 1942.

This book is a clear and simple discussion of the rôle of the hormones in reproduction, which presupposes no special knowledge of biology. There is a brief discussion of the comparative physiology of reproduction. This is followed by accounts of the estrous and menstrual cycles. The discussions of estrogens, progesterone, and the androgens contain brief historical summaries of their discovery, and accounts of knowledge of their present status. An appendix gives an account of the nature of the sterol hormones.

KOCH, F. C., AND PHILIP E. SMITH.

Edited by Biological Symposia. Vol. IX. Jaques Cattell Press, Lancaster, 1942.

Two symposia are presented in this book. The first, "Sex hormones—their actions and metabolism," contains the following papers: The comparative biology of testicular and ovarian hormones, by Carl R. Moore; The comparative metabolic influences of the testicular and ovarian hormones, by A. T. Kenyon; The metabolism of estrogens, by E. A. Doisy; The excretion and metabolism of male sex hormones in health and disease by F. C. Koch. The symposium on "Hormonal factors in the inversion of sex" contains the following: Sex inversion in the plumage of birds, by C. H. Danforth; Sex inversion in the amphibia, by R. R. Humphrey; Hormonal factors in sex inversion: the effects of sex hormones on embryonic sexual structures of the rat, by R. R. Greene; Hormones and the experimental modification of sex in the opossum.—R. K. Burns, Jr.

### ADRENALS

DORFMAN, R. I., B. N. HORWITT AND WM. R. FISH.

The presence of a cortin-like substance (colprotecting material) in the urine of normal men. *Science* 96: 496. 1942.

Ethylene dichloride extracts of pooled urine of normal men administered to adrenalectomized rats increase survival times when exposed to colchicine of 40–50%—approximately 6 hours for control to 8 to 9 hours for treated rats. Cortin-like activity was not found in urines of patients with Addison's disease.—D.A.M.

HARKNESS, D. M., E. MUNTWYLER, F. R. MAUTZ AND R. C. MELLORS.

Electrolyte and water exchange between skeletal muscle, "available (thiocyanate) fluid," and plasma in the dog following the administration of desoxycorticosterone acetate. *J. Lab. & Clin. Med.* 28: 307. 1942.

After a control period and a constant diet supplemented with 15 gms. of sodium chloride per day, ten dogs were given 1 mg. per kilo daily of doca for 14 days. As compared to the control series, there was a tendency for both plasma volume and "available (thiocyanate) fluid" to increase during the period of doca administration. At the end of the period of doca administration the plasma potassium and chloride concentrations had diminished while the sodium concentration increased. There was a similar loss of cellular potassium and increase of sodium in the muscle. There was no change in muscle chloride. Two weeks after discontinuing the drug the muscle potassium and sodium had not returned to normal levels. Despite the changes in electrolyte pattern, there was no striking change from normal in the relationship between intracellular and extracellular fluid.—B.B.R.

KOSTER, HARRY, AND LOUIS P. KASMAN.

Effect of desoxycorticosterone acetate in post-operative shock. *Arch. Surg.* 45: 272. 1942.

One hundred patients were selected alternately from 200 who had undergone surgery for conditions in which shock might reasonably be expected to develop during or after the operation. These persons were treated with desoxycorticosterone acetate and parenteral solution of sodium chloride but shock was neither prevented nor favorably influenced.—*Courtesy L. Reiner—Biol. Abst.*

PIFFNER, J. J.

The adrenal cortical hormones. *Advances in Enzymology* 2: 325. 1942.

This is a review of the chemistry and physiology of the adrenal cortical hormones with particular emphasis on the number of hormones present in the gland. Intermediary metabolism of adrenal steroids is discussed.—*D.A.M.*

## ENDOCRINE GENERAL

ALLEN, W. M., AND G. P. HECKEL.

The effect of progesterone in adolescent girls and young women with functional uterine bleeding. *Am. J. Obst. & Gynec.* 44: 984. 1942.

Results of treatment of 24 adolescent girls and young women with irregular uterine bleeding with progesterone or anhydro-hydroxyprogesterone are reported. It was observed in general that the administration of 30 mg. (5 mg. daily) of progesterone was followed by cessation of bleeding within 10 days of the last injection. Progesterone deprivation bleeding was described as occurring frequently. This is judged to explain bleeding which occurs the first few days after cessation of therapy. In about one-third of cases, cyclic bleeding occurred for 4 months or more after discontinuation of therapy whereas in about one-third of cases there were recurrences of abnormal bleeding in less than 4 months. In the other third of cases, there was amenorrhea for 2 to 3 cycles.—*E.C.H.*

FREED, S. C.

The present status of practical endocrine therapy. *Illinois M. J.* 82: 165. 1942.

Preparations of anterior pituitary are disappointing on the whole, with the exception of special high potency noncommercial growth hormone extracts in treatment of pituitary dwarfism. Chorionic gonadotropin is of definite

value in the treatment of cryptorchidism where there is no anatomical barrier preventing descent of the testes. Chorionic gonadotropin is incapable of stimulating either the monkey or the human ovary. While ovulation in the human may be produced by administration of equine gonadotropin, there is no reason to believe that any but a normal woman, who ovulates spontaneously, will respond to this substance. Its use in sterility is questionable. Its use in ovarian dysfunctions is difficult to evaluate and impractical. There is some evidence that it may stimulate spermatogenesis. Its use in the treatment of cryptorchidism is not as satisfactory as with chorionic gonadotropin. Diethylstilbestrol is highly active orally, and in dosages of 0.5 to 1 mg. a day will relieve the menopausal symptoms of a majority of patients. The main disadvantages are certain unpleasant symptoms in 10 to 20 per cent of cases. Estrogens are of the greatest value in the treatment of the menopause and complications of the menopause such as senile vaginitis and kluvarosis. They are also of value in gonorrheal vaginitis of children. In the treatment of amenorrhea, estrogens may be administered to induce uterine bleeding. In the treatment of dysmenorrhea, estrogens have been used successfully to a limited extent. Such treatment is usually temporary and repeated courses of therapy may be necessary. Injection of estrogens in oil directly into the cervix results in practically immediate control of menorrhagia in women approaching the menopause. Diethylstilbestrol and estradiol compounds have been used for this purpose. By placing 25 to 50 mg. of estrogen in crystals or pellet form in a subcutaneous pocket, menopausal symptoms may be relieved for many months without supplementary therapy because of the retarded rate of absorption. Therapeutic use of progesterone has been disappointing. It is helpful in relieving premenstrual tension and is of possible value in the treatment of habitual abortion. There is evidence, that in many cases of habitual abortion the patient has a progesterone deficiency, and on this basis progesterone may be indicated. The most efficient androgen for therapeutic purposes is testosterone propionate. Testosterone is of value in the substitution therapy of eunuchoid or castrate men. The dosages required for satisfactory effects are from 60 to 150 mg. per week. The symptoms and signs of castration return with cessation of therapy. The androgen treatment of functional cryptorchidism has few advantages, nor has it any but psychic value in treatment of senility, psychic impotence or impotence due to other than

organic causes. It should not be used for treating disorders of sperm formation since it actually suppresses spermatogenesis. This substance has been used in certain ovarian dysfunctions such as dysmenorrhea, menorrhagia, painful breasts and premenstrual tension. The amounts required are rather large, 100 to 500 mg. per month. Adrenal cortex extracts are of value in the treatment of Addison's disease, although of doubtful value in borderline cases of adrenal insufficiency such as asthenia and toxemias. Desoxycorticosterone acetate, a synthetic steroid, is effective in the treatment of Addison's disease, but overdosage may result in hypertension or even heart failure. Its use in the treatment of the borderline cases of adrenal insufficiency is open to question.—*I.B.*

KOLLER, T. H.

Estrogens in urine and blood. *Helvet. Med. acta* 9: 392. 1942.

Estrogen concentration in the urine of pregnant women slowly increases until delivery and diminishes then rapidly. There is a certain correlation between the estrogen concentration in the serum of the mother just before delivery and the size of the placenta and of the newborn. Urinary estrogen concentration of non-pregnant women is as a rule rather low during menstruation and reaches several peaks during the intervals. In patients with dysmenorrhea, estrogen in the urine is often relatively high during menstruation, but there is no correlation between uterus contractility and urinary concentration.—*Courtesy, E. Fischer—Biol. Abst.*

LISSER, H., AND ROBERTO F. ESCAMILLA.

Testosterone compounds in the male. Clinical indications and methods of administration. *Urol. & Cutan. Rev.* 46: 87. 1942.

Synthetic testosterone compounds are effective parenterally, by implantation, by inunction, orally and sublingually. The relative advantages of the several modes of administration are discussed and comparative dosages are given. The indications for testosterone therapy in the male are listed and discussed.—*Author's Summary.*

PINCUS, GREGORY, AND W. H. PEARLMAN.

Metabolism of estrone in men and non-pregnant women. *Endocrinology* 31: 507. 1942.

The estrogen titers of 3 principal phenolic fractions of the pooled urines of 8 male and 13 female patients were determined before and

after injection of estrone. The fractions were (a) the 'strong' phenolic, (b) the 'weak' phenolic non-ketonic and (c) the 'weak' phenolic ketonic. By the application of such fractions of certain partitionings between solvents and an alcoholic separation (succinic anhydride), evidence was obtained that the 3 principal urine fractions behave as though they contain estriol, estradiol, and estrone, respectively. After the injection of estrone the titer of all 3 fractions increased. The calculated recoveries indicate a conversion of the injected estrone principally to estriol, but also to estradiol. Less than 2% of the injected estrogen could be accounted for by the increased urinary excretion. Although the female patients have higher preinjection urinary titers than the male patients, the calculated recoveries of injected estrogens show no marked difference between the sexes.—*Author's Summary.*

ROCK, J., AND A. T. HERTIG.

Some aspects of early human development. *Am. J. Obst. & Gynec.* 44: 973, 1942.

Data on 12 early conceptuses obtained from 12 of 60 excised uteri in the course of a systematic search for early ova were analyzed with particular regard to: 1) the probable time of ovulation as evidenced by embryo age and endometrial histology; 2) the time of nidation; 3) the location of embedment; and 4) the frequency of abnormal ova. The ages of the embryos varied from 7 to 8 days to 16 to 17 days. From comparison of the age of the embryo with associated endometrial histology, it was apparent in two well controlled cases that ovulation occurred about 14 (13 to 15) days before anticipated menstruation. From studies of three embryos, it was concluded that nidation may take place at a variable age of the embryo (from 5th to 8th day of age) and on an endometrium which may vary in phase from the 19th to the 22nd day of a 27-day cycle. The seven normal conceptuses were found in the posterior wall of the uterus and the five abnormal ones of the anterior wall. Five (42 per cent) of the twelve embryos were so pathologic as to indicate probable early abortion.—*E.C.H.*

SNYDER, F. F.

The experimental production of toxemia of pregnancy. *Am. J. Obst. & Gynec.* 44: 1091. 1942.

At the 25th day of pregnancy 34 rabbits were given an injection of chorionic gonadotropin (dosage ranging from 10 to 144 r.u.) designed to

induce ovulation. Uteroplacental apoplexy involving premature separation of placenta was observed following this hormonal induction of ovulation.—*E.C.H.*

TWOMBLY, G. H., AND H. C. TAYLOR.

Inactivation and conversion of estrogens *in vitro* by liver and other tissues from human cancer patients and from mice of strains susceptible to mammary carcinoma. *Cancer Research* 2: 811. 1942.

When slices of liver were immersed in a watery solution of estradiol, the estrogenic activity of the hormone was diminished or destroyed. This was particularly noticeable when rat liver was used. Human liver slices did not appear to have as great a capacity for inactivated estradiol as did rat or mouse liver slices. This difference may explain why estrogens are detectable normally in human urine and not in the urine of the rat and the mouse. Tests run with livers from normal as compared with cancerous patients failed to show any consistent difference in estradiol destroying capacity. The same thing was true of the livers of 4 strains of mice differing in their susceptibility to mammary cancer.

Stronger solutions of estrone, when mixed with pregnant rabbit uterus increased their activity in such a way as to suggest that the estrone quantitatively is turned into estradiol. When malignant human tissues were compared with similar normal human tissues, this converting ability was present in only a few of both types. However, the tendency to destroy the activity of estrone by such a procedure seems to be more marked in the normal than in the cancerous tissue.—*Author's Summary.*

ZURROW, H., G. SOLAND, C. KLEIN AND S. GOLDMAN.

The effect of testosterone propionate in the treatment of arteriosclerosis obliterans. *J. Lab. & Clin. Med.* 28: 269. 1942.

Twenty-three patients suffering from arteriosclerosis obliterans were treated with biweekly muscular injections of 25 mg. of testosterone propionate. Fifteen other patients were used as controls and received biweekly intramuscular injections of 3 cc. normal saline. On the basis of author's criteria there were no significant differences between the treated and control cases with regard to the amplitude of blood vessel pulsation, arterial calcification, skin or muscle atrophy, pain while at rest, or claudication. Thus at the end of a 3-7 month period of treatment,

an 8-14 month period, and a 14-18 month period, there were no changes in functional capacity or reserve, or in anatomic conditions, as a result of treatment with testosterone propionate.—*B.B.R.*

## GONADS

BREWER, J. I.

Studies of the human corpus luteum. Evidence for the early onset of regression of the corpus luteum of menstruation. *Am. J. Obst. & Gynec.* 44: 1048. 1942.

Ninety-seven specimens from patients undergoing pelvic operations were studied. Definite regressive changes were found to appear approximately at the 8th to 10th day of the corpus luteum cycle. The regressive changes were described as follows: 1) A marked decrease in the amount of blood in the vessels of the granulosa lutein layer and regressive changes in the vascular system. 2) Fatty degeneration and degeneration by simple atrophy of the granulosa lutein cells. 3) Increase in the amount of visible lipids in the granulosa lutein cells. 4) A sharp increase in cholesterol esters and a gradual diminution of the phospholipin content, as determined chemically. 5) Regressive changes in the endometrium. 6) A decrease in the amount of pregnanediol excreted in the urine, as determined by other workers.—*E.C.H.*

CARTER, B.

A bacteriologic study of pyometra. *Am. J. Obst. & Gynec.* 44: 1074. 1942.

Endocrine interest in this article lies in reference to production of pyometra in experimental animals by injections of estrogens and in the statement that anaerobic organisms capable of invading the cervix and uterine cavity are found normally in the vaginas of postmenopausal women in a higher incidence than in the vaginas of childbearing women.—*E.C.H.*

CHUTE, R., AND A. T. WILLETS.

Treatment of cancer of the prostate with castration and administration of estrogen. *New England J. Med.* 227: 863. 1942.

Thirty-seven cases of inoperable prostatic carcinoma were treated by castration alone (2 cases), diethylstilbestrol alone (8 cases) or by combinations of the two (27 cases). General results were satisfactory, only 1 patient failing to show any improvement. Results from stilbestrol therapy alone were equal to combinations of castration and stilbestrol although improvement

lasted only during the period of treatment. Stilbestrol accelerates the effects of castration. Results included rapid, effective and lasting relief from metastatic pain, better appetite, improvement in weight and strength, feeling of well-being and reduction and softening of the prostate. In 9 of 13 cases with inability to urinate retention so improved as to urinate readily. 17-ketosteroid excretion was reduced after castration. Bony metastases, demonstrable by X-ray, progressed despite treatment. Unpleasant side-effects from stilbestrol disappeared on reduction of dosage or discontinuance of treatment.—*D.A.M.*

FELDMAN, S., J. POLLOCK AND A. R. ABARBANEL.  
Treatment of senile pruritis with androgens and estrogens: *Arch. Derm. and Syph.* 46: 112. 1942.

Twelve of 16 patients showed uniformly good results when treatment is continuous with sex specific hormone. Dosage varies with individual patients, 10 mg. of testosterone propionate or 1 mg. of estradiol dipropionate constituting an average weekly dose. In females undesirable side effects (uterine bleeding, painful nipples) are readily counteracted by combining estrogen with androgen.—*D.A.M.*

GOLDBERG, MINNIE B., AND H. LISSER.

Hypogonadism in acromegaly. Report of two cases, with improvement from male and female sex hormone. *Clinics* 1: 644. 1942.

*Case 1:* Was that of a young man 29 years of age with relatively early and mild acromegaly. He responded satisfactorily to two courses of pituitary irradiation except in respect to hypogonadism which was characterized by diminution in size of the genitalia, loss of libido and potentia; development of a peculiar sallow-yellow discoloration of the skin, markedly diminished beard growth, and a noticeable lack of vigor and strength. Testosterone propionate 25 mg. parenterally three times a week for twelve weeks resulted in return of sexual power, restoration of normal beard growth, strength and vigor, and disappearance of the fawn color of the skin. By the combination of X-ray and specific sex hormone therapy this young married man was completely rehabilitated and normalized.

*Case 2:* Was one of long-standing acromegaly (24 years) in a 44 year old unmarried woman. As a result of several surgical interventions and five courses of pituitary irradiation her acromegaly became relatively quiescent. Amenorrhea, one of the earliest symptoms in female acrome-

galics, began at the age of 20 years and had persisted for 22 years. Breasts and uterus were atrophic and the ovaries felt small and hard. She had suffered from recurrent labial herpetic ulcers. For many years she had been nervous, restless and cyclically melancholic. Under cyclic stilbestrol therapy (42 mg. per month) regular menstruation was restored (after 22 years amenorrhea), the labial ulcers vanished and the menopause-like symptoms greatly relieved.—*Author's Summary.*

GREENE, L. F., AND H. E. ESSEX.

Effects of drugs on ureteral activity. *Proc. Staff Meet. Mayo Clin.* 17: 404. 1942.

Hydrophorograph records of ureteral peristaltic activity of dogs anesthetized with barbitalurates, ether and chloralose were obtained following intravenous administration of various drugs. Epinephrine and mechoyl increase ureteral tone and peristaltic rate. Ergotoxine produced relaxation in tone and decrease in amplitude of contraction. Atropine produced inconsistent results and not in harmony with those of previous workers.—*D.A.M.*

HERBST, WM. P.

The effects of estradiol dipropionate and diethylstilbestrol on malignant prostatic tissue. *Tr. Am. A. Genito-Urin. Surgeons* 34: 195. 1941.

Seven patients with carcinoma of the prostate were treated by the administration of estradiol dipropionate or diethylstilbestrol. One mg. doses were administered, parenterally one to three times weekly for varying periods. Patients with severe pain due to osseous metastasis were almost immediately relieved of the necessity of taking opiates. There was noted a definite decrease in the total bulk of the malignant mass. In three instances where benign tissue was examined histologically after the administration of these substances, no changes could be recognized which would indicate that anything characteristic of administration of estrogen was present.

No toxic manifestations were noted except a little edema in one patient who was feeble and under treatment for hyperplasia. These symptoms cleared up with a reduction of the dose to  $\frac{1}{2}$  mg.

Breast reactions were noted in some but not in all cases and consisted of tenderness and enlargement of the breast tissues.—*D.A.M.*

Ivy, A. C.

The functional anatomy of labor, with especial reference to the human being. *Am. J. Obst. & Gynec.* 44: 952. 1942.

In this article, the author correlates the course of the wave of contraction with the morphological pattern of the uterine musculature in the human being, summarizes the evidence regarding the growth of the isthmus uteri and its unfolding and inclusion as a part of the general uterine cavity during pregnancy in the human being and monkey and reports certain observations resulting from measurements made on all the frozen sections of the human uterus reported in the literature. Endocrinology is not specifically discussed.—*E.C.H.*

LISSE, H., A. PALMER, AND D. G. MORTON.

Arrhenoblastoma—Removal followed by re-ferminization and pregnancy. *Clinics* 1: 768. 1942.

A 25 year old married housewife whose menses had been present previously ceased menstruating one year before appearance at the clinic. During this year of amenorrhea, an heterosexual hypertrichosis appeared together with hypertrophy of the clitoris. The right ovary was palpated as a freely movable cystic mass about 8 cm. in diameter. X-rays of skull, cervical spine and pelvis all showed a very slight osteoporosis. Blood pressure and glucose tolerance were normal. The sella turcica seemed normal and intravenous pyelograms yielded no evidence of an adrenal tumor. Diagnosis of arrhenoblastoma was verified surgically and pathologically. The cytological structures of the tumor varied from sarcomatoid to that of a testicular adenoma. Menstruation was restored 28 days after removal of the tumor and occurred regularly thereafter. Ten months later a positive Friedman test confirmed the suspicion of pregnancy. The abnormal hair of her face and body was of a softer texture and much of it had fallen out. The clitoris had atrophied to half of its former size.—*Author's Summary.*

MARQUARDT, C. R., AND W. A. FLAHERTY.

Carcinoma of prostate gland with special reference to endocrine treatment. *Urol. and Cutan. Rev.* 46: 343. 1942.

In forty-six patients with prostatic carcinoma an attempt was made to secure androgen suppression either by castration or administration of diethylstilbestrol. The majority of patients presented X-ray or clinical evidence of dis-

semination of prostatic growth with periprostatic involvement. Thirty-one were castrated and fifteen treated with diethylstilbestrol. Six patients entirely unimproved by castration were later given diethylstilbestrol without benefit. Likewise, six diethylstilbestrol refractory patients were castrated without improvement.

During nineteen months there have been thirteen deaths, a mortality of 30.5%. Two patients have died from pulmonary embolism, two from cardiovascular failure, one from bowel obstruction and seven from pyelonephritis. One patient with hypertension died six months after castration from apoplexy. This patient had marked clinical improvement following castration and had X-ray evidence of improvement in his metastatic bone lesions.

Sixty per cent of all patients treated showed clinical improvement as evidenced by relief of urinary obstruction and pain, gain in weight and improved blood picture. The prostate as palpated per rectum has decreased in size and became noticeably softer.—*Author's Summary.*

ROBSON, J. M., AND A. SCHÖNBERG.

A new synthetic estrogen with prolonged action when given orally. *Nature, London* 150: 22. 1942.

$\alpha$ -di(p-ethoxyphenyl)  $\beta$ -phenyl bromoethylene in oil when injected subcutaneously in 4 doses over 48 hours into ovariectomized mice or when administered orally in single doses exerts a much more prolonged estrogenic action than diethylstilbestrol, estradiol dipropionate, triphenyl chlorethylene or other estrogenic substances.—*D.A.M.*

WINN, W. C., AND H. HUDNALL WARE.

Hydatidiform mole. *Virginia M. Monthly* 69: 678. 1942.

In several cases of hydatidiform mole, the spinal fluid gave a negative test for gonadotropin by the rabbit ovulation test, although the urine was positive. Positive rabbit ovulation tests with urine were obtained as long as 4 and 7 weeks postoperatively in 2 patients.—*Courtesy R. J. Main.—Biol. Abst.*

## HYPOPHYSIS

ESCAMILLA, ROBERTO F., AND H. LISSE.

Testosterone therapy in a male case of hypophyseal cachexia (Simmonds' disease). *Clinics* 1: 710. 1942.

Testosterone therapy had a decidedly beneficial effect in a characteristic case of Simmonds' disease caused by a craniopharyngioma. Partial removal and drainage of the Rathke's pouch cyst relieved increased intracranial pressure but did not favorably influence pituitary function. Six months later, at the age of 20 years, testosterone therapy was started and during the subsequent 19 months of treatment, this young man grew  $1\frac{3}{4}$  inches and gained  $23\frac{1}{4}$  pounds. Prior to treatment his height was 5 feet  $4\frac{3}{4}$  inches (164 cm.) and his weight 67 pounds (30.5 kg.). Normal sexual function appeared and the genitalia enlarged considerably. The secondary sexual characteristics improved also. The patient's general strength and vigor were strikingly benefited.

It is significant that the excellent result achieved represents the satisfactory use of a potent hormone not derived from the endocrine organ primarily responsible for the endocrinopathy—namely, testosterone as an aid in combatting a severe panhypopituitarism.—*Author's Summary.*

ROCHAT, R. L.

Simmonds' disease and amenorrhea following fetal hypophyseal grafts. *Helvet. med. acta* 9: 373. 1942.

A 23 year old girl with Simmonds' disease (pituitary cachexia) was considerably improved by intramuscular implantation of a fetal hypophysis. The patient increased in weight during 4 months from 42 to 51 kg., her basal metabolism returned to normal values, and the first menstruation occurred after  $6\frac{1}{2}$  years of complete amenorrhea.—*Courtesy, E. Fischer—Biol. Abst.*

## PANCREAS

JOSLIN, E. P.

The use of insulin in its various forms in the treatment of diabetes. *Bull. New York Acad. Med.* 18: 200. 1942.

A review of the forms of insulin in use today in treatment of diabetes, with reasons for preferential use of certain forms.—*D.A.M.*

## PARATHYROID

ROSS, WM. F., AND THOMAS R. WOOD.

The partial purification and some observations on the nature of the parathyroid hormone. *J. Biol. Chem.* 146: 49. 1942.

A method is described for the preparation of

parathyroid extracts of approximately 3 times the activity of any hitherto reported. Present concepts regarding the protein nature of the active principle are reinforced by a study of its pepsin digestion under suboptimal conditions, by its ultraviolet absorption spectrum, and by its stability to electrodialysis. Ultracentrifugal study of the preparation shows it to be heterogeneous, consisting of at least 2 components, 1 of molecular weight of roughly 20,000 and another of 500,000 to 1,000,000. There is some reason to believe that the activity may be associated with the low molecular material.—*Author's Summary.*

## THYROID

BARTLETT, WILLARD.

Essential biochemical derangements in hypothyroidism. *Arch. Surg.* 45: 103. 1942.

The correlation between thyrotoxicosis and acidosis was studied. The carbon dioxide-combining power of the plasma of 18 patients who were resting and whose physiological needs for water and nourishment were met, was maintained within normal limits even in severe exacerbations, but on exertion a prompt decrease in alkali reserve occurred. In 8 of 18 patients who showed prompt improvement after thyroidectomy a measurable rise in alkali reserve was observed. During improvement on treatment preliminary to thyroidectomy and subsequent operation, the total titratable acid of the urine of the organic acids and of ammonia fell considerably and the pH of the urine rose. The patient's intake of food was kept constant quantitatively and qualitatively. The bearing of these findings on the pathology and symptomatology of hyperthyroidism was discussed.—*Courtesy J. Reiner—Biol. Abst.*

HIMWICH, H. E., C. DALY, J. F. FAZEKAS AND H. C. HERRLICH.

Effect of thyroid medication on brain metabolism of cretins. *Am. J. Psychiat.* 98: 489. 1942.

The brain metabolism of 11 cretins ranging in age from 9 to 31 years was studied before and after administration of desiccated thyroid. Alterations of brain metabolism were determined by taking into consideration the changes of the arterio-venous  $O_2$  difference and cerebral blood flow which was estimated with the aid of a thermostromuhr inserted in the internal jugular vein. Blood was collected from an artery and the internal jugular vein and analyzed for  $O_2$ . The average of 29 arterio-venous  $O_2$  differences of 11

cretins was 5.74 vol % before thyroid administration and that value was reduced to 4.69 vols % on 25 observations on 9 patients after therapy. In 8 cretins the average acceleration of cerebral blood flow was 57%. An average increase of 32% in cerebral metabolism was thus revealed as a result of the administration of thyroid. This increase in cerebral metabolism afforded a basis for alterations in the cerebral electrical potentials and psychological reactions of these patients. The electroencephalograms disclosed a rise of the energy level in certain frequency ranges. Psychologically, improvement was either absent or of questionable significance in any of the higher processes. The greatest change was that of an acceleration of psychological activity, an acceleration made possible by the increased energy expenditures stimulated by thyroid medication.—*Courtesy B. L. Pacella—Biol. Abst.*

KING, EARL J., AND C. G. BARNS

Galactose tolerance in thyrotoxicosis. *J. Path. and Bact.* 54: 526, 1942.

Less than 8% of normal subjects have a galactose index over 120. In 37 thyrotoxic patients the index was over 120 in all except 4 very mild cases. (The galactose index is the sum of the blood galactose values in mg at  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$  and 2 hours after the injection of 40 g of galactose).—*Author's Summary*

MAN, E. B., A. E. SMIRNOW, L. F. GILDER, AND J. P. PETERS

Serum iodine fractions in hyperthyroidism. *J. Clin. Invest.* 21: 773, 1942.

Protein bound iodine was separated from inorganic iodine in serum by precipitating with the Somogyi reagent used for preparation of blood filtrates. Iodine in the precipitate and filtrate was determined by the permanganate acid ashing technique. When solutions of diiodotyrosine or thyroxine were added to serum the precipitate from serum contained at least 80% of diiodotyrosine iodine and virtually all thyroxine iodine.

The precipitable iodines of 6 normal subjects given 10 to 45 drops of Lugol's solution daily for 1 to 7 days agreed within 1.6 gamma per cent with serum total iodines after Lugol's administration was stopped. In normal individuals after cessation of iodine administration, 2 days, but occasionally 4 to 10 days, were necessary for elimination of excess inorganic iodine from the serum.

Precipitable iodines were studied in 15 hyperthyroid patients whose clinical diagnosis was confirmed by pathological study of the glands. Before treatment with iodine, serum total or precipitable iodines were between 9.4 and 33.7 gamma per cent per 100 cc, distinctly above the normal range of 4 to 8 gamma per cent. In 5 patients, before administration of iodine, total and precipitable iodines agreed within 2.0%. After Lugol's, before thyroidectomy, precipitable iodines of 11 of 14 patients decreased to about 8.0 gamma per cent. In 3 patients, whose precipitable iodines did not decrease noticeably, clinical response to iodine administration was poor. If basal metabolisms are unsatisfactory, the behavior of the precipitable iodine is of diagnostic significance.

Serum total or precipitable iodines of 10 of 15 patients were within or just above the normal range about 2 weeks after thyroidectomy.—*Author's Summary*

PRITTLER, D. B., AND A. G. MARTIN

Diagnosis and surgical treatment of goiter. *Med. Clin. N. America* 26: 1739, 1942.

This is a brief discourse on the diagnosis and treatment of the common types of thyroid enlargements from the surgical viewpoint, with illustrative case histories. The conditions emphasized are exophthalmic goiter, toxic and nontoxic adenomas, and thyroiditis. The possible harmful effect of iodine administration is stressed. The general methods of diagnosis, preparation, and postoperative care for colloid goiter, diffuse toxic goiter, nodular goiter, both toxic and nontoxic, and thyroiditis are discussed. At the present time, definitive treatment of the great majority of thyroid disorders means surgical treatment. However, there is more to the treatment of thyroid disease than operation alone. Cardiac, nutritional and endocrine factors call for close cooperation between internist and surgeon throughout the treatment of thyroid disease.—*I. B.*

PICARDO, T., AND G. NARANJO

Treatment of hyperthyroidism. *Rev. Med. (San Jose)* 5(96): 175, 1942.

The authors describe a new treatment for hyperthyroidism. It consists in giving subcutaneous injections of beef thyroid peptone (5%) over a period of months. They cite one case in which a total of 50 cc (2.5 gm peptone) was given for



4 months. The patient's pulse rate was lowered, she gained weight and the exophthalmos was definitely reduced. This type of treatment has several advantages over previous treatments. The extract is not antigenic. It acts specifically against the thyrotropic hormone, and does not neutralize the effect of other hypophyseal stimuli. Repeated injections do not lead to hypertrophy of the thyroid.—*Courtesy E. McNeil, Biol. Abst.*

ROSE, E.

The diagnosis and treatment of thyroid disease. *Med. Clin. N. America* 26: 1711. 1942.

Hypothyroidism often masquerades in a variety of clinical disguises. The optimal dose of desiccated thyroid varies from patient to patient. The same brand of thyroid substance should be used throughout the course of any given case. The treatment of hypothyroidism should not be abandoned because of the appearance of signs of overdosage. Hyperthyroidism often simulates other diseases and other diseases may simulate hyperthyroidism. Subtotal thyroidectomy competently performed after proper preparation is the best single method of treating hyperthyroidism. Irradiation is useful in carefully selected cases. The beneficial effect of iodine in hyperthyroidism is usually temporary. The principal use of this drug should be in the preparation of patients for thyroidectomy. Nontoxic diffuse goiter seldom responds completely to iodine therapy, but such therapy is justifiable because of its occasional good results and possible prophylactic effect. Nontoxic nodular goiters should be treated surgically unless special contraindications exist.—*Author's Abst.—I.B.*

ROSENKRANTZ, J. A., MAURICE BRUGER AND A. J. LOCKHART.

Studies on galactose tolerance with especial reference to thyroid disease. *Am. J. M. Sci.* 204: 36. 1942.

Age alone has no influence on the galactose tolerance curve. Impaired galactose tolerance occurred in hyperthyroidism, Bright's disease, upper respiratory infections, malignancy, and as a concomitant finding of sulfonamide therapy. The impairment was most marked in thyrotoxicosis. Diabetic patients have a normal tolerance.—*C.P.*

SCHMIDT, C. R., A. E. HERTZLER.

Cardiotoxic goiter—a distinct entity. A preliminary report. *Endocrinology* 31: 684. 1942. The present day concept that chronic hyper-

thyroidism is due to excessive activity of normal glandular tissue fails to explain the normal or slightly elevated basal metabolic rate in the majority of patients with goiters of long duration. Three types of experimental evidence suggest that goiters produce a perverted rather than an excessive secretion. The colloid from degenerated and nodular goiters associated with cardiac symptoms show changes in the staining properties of the colloid: with hematoxylin-eosin certain follicles stain basophilic instead of acidophilic; with Mallory's aniline blue dye these areas stain orange instead of the usual deep blue. Chemical analysis of thyroglobulin reveals that a goiter is incapable of both storing and synthesizing thyroxine in normal amounts. Extract from toxic goiters contains a principle which, when fed to thyroidectomized rats, causes an increased heart rate without a corresponding increase in  $O_2$  consumption.—*Author's Summary.*

SEARLE, H. H.

Thyroid disease. Experiences and conclusions of a thyroid committee. *California & West. Med.* 57: 184. 1942.

The nodular goiter presents a dangerous threat of malignant degeneration and therefore demands removal. Toxic diffuse goiter may be treated by partial ablation either surgically or by X-ray. Iodine should be used in toxic goiter only before surgery. Resection should be more radical in children than in adults. In experienced hands, mortality rate in thyroid surgery approaches zero and complications are rare.—*M. L. Ilsley (Biol. Absts.).*

SOLEY, M. H.

Exophthalmos in patients with various types of goiter. *Arch. Int. Med.* 70: 206. 1942.

In nontoxic nodular goiter the eyes of patients are not more prominent than those of normal persons (Hertel exophthalmometer). Patients with toxic nodular goiter tend to have more prominent eyes than normal persons but not so prominent as in patients with toxic diffuse goiter. The eyes of patients with toxic diffuse goiter are significantly more prominent than those of normal persons. Exophthalmos becomes significantly greater following subtotal thyroidectomy in over 50% of patients with toxic diffuse goiter. At the same time the majority lose the stare associated with hyperthyroidism. If patients with toxic diffuse goiter receive X-ray treatment, the progression of exophthalmos occurs to a lesser degree and less frequently than in the group in whom a subtotal thyroidectomy is done.—*Author's Abst.*

# The Journal of CLINICAL ENDOCRINOLOGY

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## A Diurnal Rhythm in the Excretion of Urinary Ketosteroids by Young Men<sup>1</sup>

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THE PRESENCE of a diurnal cycle in the urinary output of 17-ketosteroids might have some consequence in consideration of their functional significance. The marked quantitative changes in excretion accompanying various pathologic states (1, 2) may indicate that the processes involving ketosteroid secretion may be labile to ordinary daily stresses.

### SUBJECTS AND METHODS

Seven young men ranging in age from 22 to 29 years undertook the collection of consecutive night and day urine specimens for periods ranging from 5 to 9 days. In most cases the attempt was made to collect 4 specimens for each 24-hour period, but this was not always possible.

Toluol was added as preservative and the urines hydrolyzed and extracted within 48 hours of collection. Our usual method of acid hydrolysis and ether extraction was practiced (3). The dried neutral fractions of the ether extract were separated into ketonic and non-ketonic fractions by the micro-Girard reaction

(3). Determinations of the 17-ketosteroid titer were made upon the ketonic fractions by the aqueous alcohol technique previously described (3) except that the aliquots were incubated in the dark for one hour, instead of 45 minutes. All results are expressed in terms of mg. equivalent of 17-ketosteroid per hour. 'Night' values are for specimens representing the period of sleep, ranging from 8 to 12 hours; 'day' values are the means for the total waking hours.

### RESULTS

In table 1 are presented the data on the mean day and night values for 17-ketosteroids and the corresponding urine volume outputs. It is evident from the data that *a*) the night values for 17-ketosteroid output are consistently lower than the day values for all subjects; *b*) each individual tends to have a characteristic level of 17-ketosteroid excretion for both night and day; *c*) there is a rough, but far from regular, tendency for the level of 17-ketosteroid excretion to parallel the urine volume output.

In figure 1 are presented graphically the data on specimens taken regularly during the collection period for two subjects (*B* and *D*). The data on the last day's collection for *subject*

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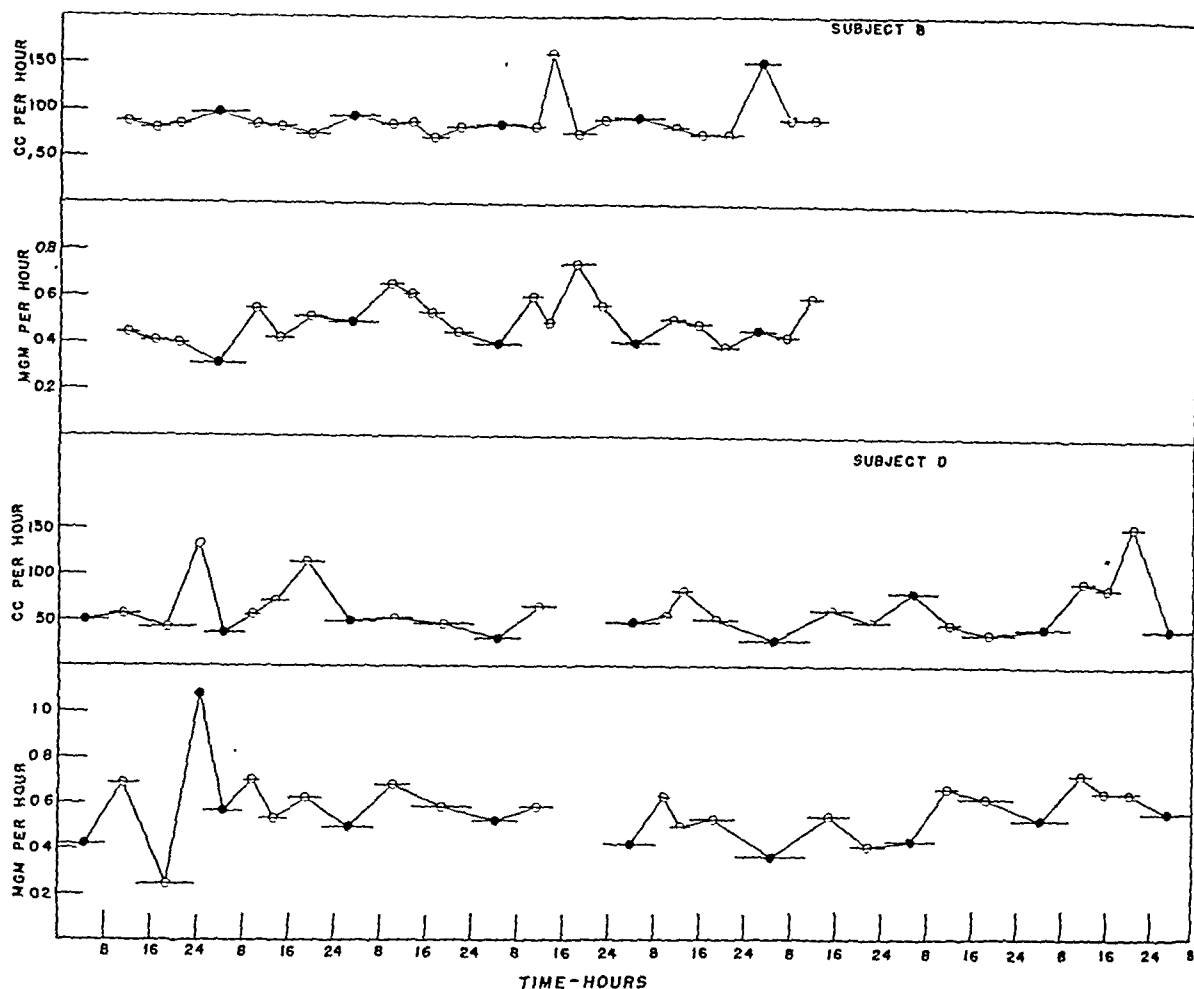


Fig. 1. Data on the rate of 17-ketosteroid and urine output for two subjects. The horizontal bars indicate the time of collection which each urine specimen represents. Time is given on a 24-hour clock, in which 24 is midnight.

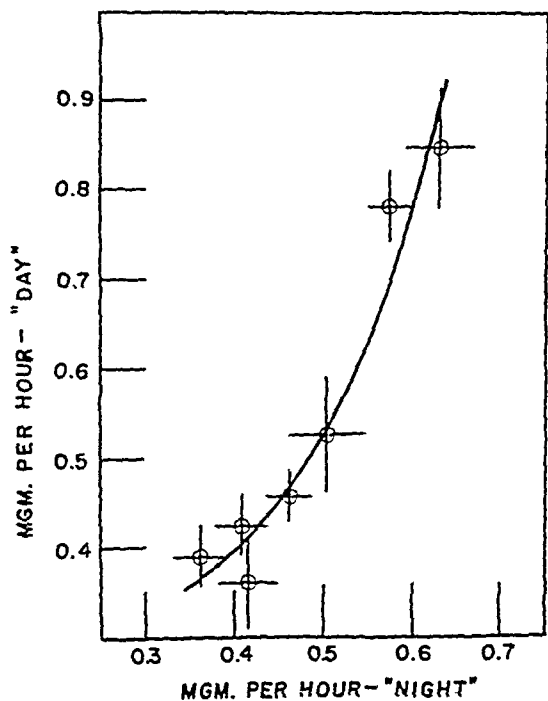


Fig. 2. The mean day value for 17-ketosteroid output is plotted against the mean night value for each of the 7 subjects. The horizontal bars represent

*D* are omitted. Inspection of this figure reveals a) the tendency for 17-ketosteroid excretion to be at a minimum in the specimens taken at night; b) a tendency for the maximum 17-ketosteroid excretion to occur in the morning hours. The fourth specimen taken from subject *D* covered a period of a little over an hour when the subject was awakened and asked to take an emergency call on a hospital ward; the high level of both 17-ketosteroid and urine volume output should be noted. Data on the five other subjects exhibit the same general diurnal fluctuations.

On figure 2 the relation between mean 17-ketosteroid output during the day is plotted against the mean night value. These data indicate the possibility of a regular relationship between day and night excretion levels.

sent  $\pm$  the standard error for the night values, the vertical bars  $\pm$  the standard error for the day values. See table 1.

The rough parallelism between urine volume and 17-ketosteroid output led to the test of the possibility that the 17-ketosteroids increase in amount during the day simply by being flushed

the soup and milk being taken at the end of the ingestion period. The diuresis ensuing was quite marked, but no significant increase in 17-ketosteroid excretion occurred during the

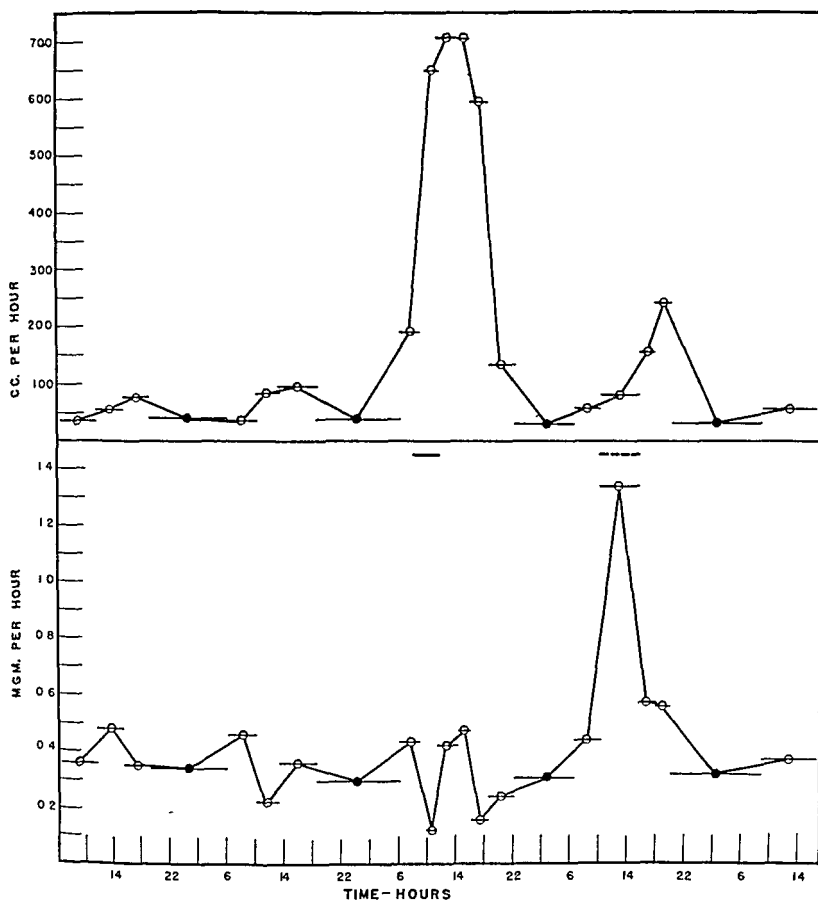


Fig. 3. A forced diuresis experiment on *subject D*. Data on 4 days' collections are plotted as in figure 1. The solid bar represents the period of ingestion of 6.2 liters of fluid, the broken bar a period of emergency hospital duty (see text). Time is given on a 24-hour clock in which 24 is midnight.

out of the kidneys. *Subject D* undertook a forced diuresis experiment, the data of which are presented graphically in figure 3. After two days of control collections, he ingested, over a period of 3.5 hours, 6.2 liters of fluid of which 5.0 liters was water, 0.6 was soup and 0.6 milk,

period of diuresis. One specimen, in fact, gave an abnormally low value; this was taken during a brief period following mild signs of water intoxication. At approximately 24 hours after the period of high water intake the subject was called upon for emergency hospital duty which

lasted through his lunch hour well into the afternoon. The specimen covering this 7.5-hour period gave an unusually high 17-ketosteroid titer, approximately 2.5 times that usually obtained during that time of day. The two succeeding specimens showed slightly elevated 17-ketosteroid titers and increased urine output.

DISCUSSION

Five of the subjects (*A*, *B*, *D*, *F* and *G*) exhibit a statistically significant difference between the night and day values of 17-ketosteroid excretion (table 1), and the data of

indicate that the stress of daily duties tends to elevate the 17-ketosteroid output. Alternatively, we may attribute the increase simply to activity. On two occasions, emergency calls not involving excessive physical exertion induced extreme increases in output; this may indicate tension rather than activity as the cause of the ketosteroiduria and the accompanying diuresis. Since no special control of water intake was practiced by these subjects, the exact relation between urine volume and 17-ketosteroid output cannot be defined. Nonetheless, the forced diuresis experiment indicates that diuresis, *per se*, is not a cause of ketosteroid-

TABLE 1. THE MEAN DAY AND NIGHT VALUES OF 17-KETOSTEROID AND URINE VOLUME OUTPUTS FOR 7 SUBJECTS<sup>1</sup>

Subject	No. of 24-Hour Periods	17-Ketosteroid Titer, mg. per hour		Urine Volume Output, cc. per hour	
		Night	Day	Night	Day
<i>A</i>	7	0.362±0.029	0.489±0.033	27.2±2.7	47.2± 1.9
<i>B</i>	6	0.409±0.030	0.523±0.035	42.9±1.9	37.5± 3.9
<i>C</i>	6	0.416±0.033	0.460±0.051	22.4±3.0	20.9± 2.5
<i>D</i>	9	0.462±0.026	0.557±0.029	42.4±3.0	62.2± 6.8
<i>E</i>	5	0.504±0.042	0.627±0.065	39.6±8.9	53.4± 6.7
<i>F</i>	7	0.574±0.024	0.882±0.040	33.0±2.3	73.1±11.5
<i>G</i>	8	0.630±0.037	0.948±0.068	44.8±4.1	60.0± 3.1

<sup>1</sup> The standard errors indicated are calculated by the formula: S.E. =  $\pm \sqrt{\Sigma d^2 / n(n-1)}$ .

two subjects (*C* and *E*) in which the lowered night excretion is not statistically significant exhibit the same trend. It is obvious, therefore, that the data as a whole indicate overwhelmingly an increased 17-ketosteroid output during the waking hours. Although Bachman, *et al.* (4), were unable to detect a statistically significant difference in 17-ketosteroid output between successive 12-hour specimens in two women, it should be pointed out that their data do not necessarily apply to men and that their collections were made at 8 A.M. and 8 P.M., respectively, presumably covering in each case a number of waking hours. The rise occurring in the 'day' excretion of these subjects would therefore indicate the need of caution in the use of short-interval collections of urine for clinical routine studies. The night values of 17-ketosteroids for all of these subjects exhibit consistently a lower standard deviation (see table 1) than do day collections and night specimens may therefore be more reliable in setting up a standard.

The data of this paper may be interpreted to

uria. Bachman, *et al.* (4), found similar indications of the independence of urine volume and 17-ketosteroid output in women.

The fact that, over the periods studied, each individual exhibits a characteristic level of 17-ketosteroid excretion deserves more than passing attention. The differences between the means for the night specimens for *subject A* and *subjects D* to *G* are, for example, statistically significant. The day values are more variable, but the mean values for *subjects F* and *G* differ significantly from those of *subjects A* to *E*. We have been unable to correlate age, weight or physical conformation with the observed values. The relative constancy of individual excretion levels has been noted by Fraser, *et al.*, (1) and by Werner (5), but has not been statistically defined by these authors. In view of the fact that their data are derived from determinations made upon the total neutral fractions and not upon the ketonic neutral fractions of urine, comparisons are difficult.

Superficially, the only resemblances between

our subjects excreting 17-ketosteroid at comparable rates seem to involve considerations of temperament and nervous tension. The probability that the 17-ketosteroid excretion is an index of adrenal steroid secretion (1, 6, 7) offers an interesting basis for suggesting a neuro-endocrine mechanism.

#### SUMMARY

Urine specimens were collected regularly from 7 young men over a total of forty-eight 24-hour periods, and records were made of the 17-ketosteroid and urine-volume outputs on all specimens collected throughout these periods. The night values for 17-ketosteroids are regularly lower than the day values; the maximum day value tends to occur in specimens taken during the morning hours. High night titers appear to be associated with high day

titers and vice versa. Forced diuresis did not significantly increase the rate of 17-ketosteroid excretion in one subject; emergency calls in the hospital were associated with significant titer increases in this subject.

*Acknowledgment* I am much indebted for technical assistance to Mr. Irving Weiss. The special cooperation of Lt. E. B. Romanoff is gratefully acknowledged.

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4. BACHMAN, C., D. LEEKLEU AND B. WINTER: *J. Clinical Endocrinology* 1: 142. 1941.
5. WERNER, S. C.: *J. Biol. Chem.* 136: 483. 1940.
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TABLE 3. DEVIATION IN THE AMOUNT OF 1.783 MG. OF TRANS-DEHYDROANDROSTERONE RECOVERED FROM 250 CC. OF DISTILLED WATER BY A 10 MINUTE REFLUX PERIOD WITH 75 CC. OF CCl<sub>4</sub>

Amount Recovered by CCl <sub>4</sub> Extraction	Percentage Recovery
mg.	%
1.617	90.3
1.654	92.5
1.639	92.0
1.676	93.8
1.631	91.3
1.631	91.3
1.713	96.2
1.649	92.4
	92.5 mean

samples of urine extracted for 10 minutes were then re-extracted for one hour with fresh 75-cc. quantities of CCl<sub>4</sub> and the additional amounts of hormone recovered are shown in column 3. Table 3 shows another determination of the efficiency of the CCl<sub>4</sub> extraction. Ten-cc. portions of 95 per cent ethanol solution of crystal-

TABLE 4. DEVIATION OF ANALYTICAL RESULTS

Sample 1 mg./250 cc.	Sample 2 mg./250 cc.
1.54	1.45
1.55	1.50
1.56	1.53
1.53	1.49
1.545 mean	1.492 mean
0.97% maximum deviation	2.68% maximum deviation

17-ketosteroids from 250 cc. portions of two urine samples hydrolyzed and refluxed as described in text. The figures represent 17-ketosteroids recovered as mg. of dehydroisoandrosterone.

line trans-dehydroandrosterone were added to 250-cc. quantities of distilled water. The samples of water containing the hormone were refluxed for 10 minutes with 75-cc. amounts of CCl<sub>4</sub>. The CCl<sub>4</sub> was then separated from the water, evaporated and the amount of hormone extracted determined as outlined above.

The preciseness of the determination of the hormone content of identical 250-cc. samples of urine is shown in table 4. Two 1-liter samples of urine of normal males were each divided into 250-cc. portions, then hydrolyzed and extracted as described in the method above.

*Washing.* The variation involved in the process of washing the CCl<sub>4</sub> extract with 10 per cent NaOH solution and water is indicated by the figures given in table 5. Three hundred cc.

of CCl<sub>4</sub> extract from urine from normal male was divided into 4 portions and each of them was washed in separatory funnels with 10 per cent NaOH and water as described in method.

To determine the effectiveness of a strong alkali wash in removing estrogens the following experiment was performed. One 75-cc. portion of CCl<sub>4</sub> extract of urine obtained during eighth month of pregnancy was washed once with 10 per cent NaOH and 3 times with water. A second identical sample was washed 4 times

TABLE 5. DEVIATION IN RESULTS OF WASHING FOUR IDENTICAL PORTIONS OF A CCl<sub>4</sub> EXTRACT WITH WATER AND 10 PER CENT NaOH SOLUTION

17-ketosteroids mg./75 cc. of CCl <sub>4</sub>
1.22
1.24
1.25
1.24
1.237 mean
1.4% maximum deviation

with NaOH and 3 times with water. A third sample was washed with NaHCO<sub>3</sub>, NaOH, and water as recommended by some investigators (3). The amount of hormone determined is shown in table 6.

When a CCl<sub>4</sub> extract of urine is shaken in a separatory funnel with either water or NaOH solution, there is sometimes a layer of emulsion which may remain at the interface after the layers of solvent and washing solution have separated. This will disappear if the funnel is allowed to stand for a long time, but the amount of solvent saved by this practice is insignificant. Eight 75-cc. urine extracts were washed once with water, once with NaOH and twice more with water, leaving only half a minute or so each time for the two layers to separate. All of the washing solutions used

TABLE 6. EFFECT OF VARIOUS METHODS OF WASHING CCl<sub>4</sub> EXTRACT OF URINE SPECIMEN IN EIGHTH MONTH OF PREGNANCY

Method of Washing			17-Ketosteroids Recovered mg./250 cc urine
NaHCO <sub>3</sub>	10% KOH	Water	
	1 time	3 times	1.80
	4 times	3 times	1.64
2 times	4 times	3 times	1.65

were saved and allowed to stand until the solvent left in them had settled out, and this was then measured. For the 600 cc of  $\text{CCl}_4$  washed the amount of  $\text{CCl}_4$  recovered from the washings was 67 cc., or a loss for each urine extract of only about 1 per cent of the original volume.

**Color development.** The 1-cc. quantities of standard dehydroisoandrosterone and urine extract solutions are measured with 1-cc. pipettes. The alcoholic KOH and the *m*-dinitrobenzene solutions do not need to be measured so precisely and a 10-cc. graduated pipette is more convenient. A 25-cc. graduate is used to measure the alcohol for the final dilution. Table 7 lists the electrophotometer readings of 10 identical tubes of standard dehydroisoandrosterone solution prepared as described.

TABLE 7 VARIATION IN ELECTROPHOTOMETER READINGS OF TEN TUBES OF IDENTICALLY PREPARED URINE EXTRACT SOLUTIONS

Electrophotometer Readings		
43.5	43.5	
43.6	43.5	
44.0	44.7	mean = 43.94
44.3	44.3	max. deviation = 0.80 or 1.8%
44.2	43.8	

Readings are from the logarithmic scale of the Fisher electrophotometer.

If 25 cc. of 95 per cent alcohol is added to the tube containing the reaction mixture there is sometimes a turbidity due to carbonate precipitation. The use of 70 per cent alcohol eliminates this cloudiness and also conserves alcohol. Table 8 gives electrophotometer readings of samples of 0.2 mg./cc. dehydroisoandrosterone solutions that had been allowed to react with alkaline *m*-dinitrobenzene and were then diluted with 25-cc. quantities of 95 to 55 per cent ethanol. The amount of color is the same for any dilutions of alcohol between 95 and 55 per cent. The amount of fading occurring in a half-hour period after dilution is no greater with the low concentration than with the high.

As a check on the method of color development and determination (4) four portions of an alcoholic solution of urine extract, from 0.25 to 2.0 cc in volume, were placed in test tubes. The alcohol was then evaporated off, 1 cc of

TABLE 8. ELECTROPHOTOMETER READINGS OF DEHYDROISOANDROSTERONE SOLUTIONS THAT HAVE BEEN ALLOWED TO REACT WITH ALKALINE *m*-DINITROBENZENE REAGENT AND THEN DILUTED WITH VARIOUS CONCENTRATIONS OF ETHANOL

Concentration of Ethanol Used for Dilution, %	Electrophotometer Readings with No. 525 Filter		
	Extract reading	Reagent blank reading	Corrected extract reading
95	45.3	9.6	35.7
85	44.7	9.0	35.7
75	44.0	8.7	35.3
65	43.9	9.3	34.6
55	43.9	8.3	35.6

Readings are from the logarithmic scale of the Fisher electrophotometer

alcohol was replaced, and the color was developed and measured in the usual way. The 17-ketosteroid determinations are shown in table 9.

## DISCUSSION

Simultaneous hydrolysis and extraction with heated  $\text{CCl}_4$  has been reported (5), but the data shown in table 1 indicate that even when the urine is kept at the boiling point of  $\text{CCl}_4$  the hydrolysis with 10 per cent acid is slow. Three hours of simultaneous hydrolysis and extraction is necessary to recover as much 17-ketosteroid as comes out in 5 minutes with a previous 10-minute hydrolysis at 100° C. When the urine was acidified to 15 per cent HCl and simultaneously refluxed and extracted for 15 minutes the yield was no greater than with 10 per cent acid.

The long extraction period necessary for the removal of 17-ketosteroid from urine has been one of the chief factors that makes the determination time-consuming. Hershberg (6) reported the use of a rapid extractor in which  $\text{CCl}_4$  is allowed to drop through a sintered glass disc into a column of urine heated by an electric coil. One-half hour of extraction is reported to be sufficient. The reflux method used

TABLE 9 COLORIMETRIC DETERMINATION OF VARIOUS AMOUNTS OF A SINGLE URINE EXTRACT

Amount of Urine Extract	17-Ketosteroid as Dehydroisoandrosterone	Concentration Ratio
cc	mg	
0.25	0.033	1.00
0.5	0.069	2.09
1.0	0.134	4.08
2.0	0.272	8.24



by the present authors takes even less time than this. The hot water baths keep the urine at about the boiling point of  $\text{CCl}_4$ ,  $76^\circ \text{C}$ ., and the solvent makes efficient contact as the droplets rise and fall through the aqueous layer and as the  $\text{CCl}_4$  condenses and runs down the sides of the flask.

A reflux method using  $\text{CCl}_4$  has been outlined by Sachs and Kurzrok (7) in which the urine is refluxed with three changes of  $\text{CCl}_4$  for a 6-hour period, but the process is much longer and no measure of its efficiency is given.

The rapidity with which 17-ketosteroids are removed from urine by the outlined method is indicated by table 2. Four hours of refluxing with  $\text{CCl}_4$  resulted in recovery of only 5 per cent more hormone than was obtained by 10-minute extraction. Re-extraction of the 10-minute samples with fresh  $\text{CCl}_4$  produced about 10 per cent additional chromogenic material. These figures seem to indicate that at least 90 per cent of the hormone is removed from the urine in the 10-minute extraction period. This is further substantiated by the results presented in table 3, which show that an average of 92.5 per cent of the amount of crystalline hormone added to distilled water can be recovered by a 10-minute extraction. The range for the eight extractions listed was less than  $\pm 4$  per cent.

Most investigators have used either a one-liter sample or a full 24-hour urine specimen for 17-ketosteroid determinations. It is not only more convenient to use smaller portions but there is a considerable saving of solvent and acid. Table 4 shows that the hormone content of samples of urine as small as 250 cc. can be measured precisely. In the four determinations on one sample of urine the greatest deviation from the mean value of hormone recovered was less than 3 per cent. For the other sample it was less than 1 per cent.

The variation involved in washing several 75-cc. samples of  $\text{CCl}_4$ -urine extract is slight enough to be non-significant. This is indicated by the figures in table 5 which show that the greatest deviation from the mean value of four similar determinations was only 1.4 per cent.

Washing urine extracts with a 10 per cent  $\text{NaOH}$  solution removes certain yellow and brown pigments which may otherwise give

high blank readings. Estrogens may interfere with the test if they are not removed because they give a color similar to that of androsteron with the m-dinitrobenzene reagent. Since these are weak phenols the alkali washing takes them out. It seems a loss of time to wash the extract repeatedly for this purpose, however, because the amount of estrogen excreted by women in any 24-hour period is usually too slight to detect by the chemical test. For the whole menstrual cycle the quantity of estrogen excreted is less than 1 mg., and even for the day of highest excretion the value is not much over 0.1 mg. (8). During pregnancy the excretion of estrogen in the urine is greatly increased but even with this greater amount the error possible with only one alkali washing is slight. As shown by the data in table 6 the hormone recovered from a sample of  $\text{CCl}_4$  extract of pregnancy urine washed 4 times with alkali is only 9 per cent less than that from one washed once and some of this loss may have been due to the washing process rather than to the selective removal of estrogen.

It is convenient and rapid to use standard laboratory pipettes for measuring the hormone solutions and reagents in the colorimetric determination. Use of 1-cc. quantities instead of the 0.2-cc. amounts employed by most other investigators makes this possible. Table 7 shows that the electrophotometer readings on 10 identical preparations of a urine extract sample set up in this manner have a mean deviation of less than 1 per cent and a maximum of less than 2 per cent from the average reading.

Some clinical laboratories may not have an accurately controlled  $25^\circ \text{C}$ . water bath in which to keep the tubes while the color is developing. Even if this equipment is available there still may be variations in the time required for manipulation of the tubes before they are read in the colorimeter and in the amount of color developed in the reagent blank. It is, therefore, about as convenient and often more accurate, to prepare tubes of standard hormone solution and of reagent blank mixture and make the calculations as outlined in the method, rather than compute the results by interpolation on a previously prepared curve.

Table 9 presents an experimental check of the preciseness of the outlined method for developing color in the hormone solution by the alkaline m dinitrobenzene reaction. Although the range of concentrations tested was eight fold the maximum variation from the theoretical for any sample was only a  $\pm 2$  per cent.

Urine contains certain non ketonic materials that give interfering yellow color. This fraction of the total chromogenic substance is normally slight, 0.3 to 2.4 mg/24 hr (9) and is usually considerably less than the daily variation. However, if the 17-ketosteroid excretion is low, its interfering fraction may make up a large portion of the total. The non ketonic fraction may be eliminated by means of the Girard reagent (5), but this process adds considerably to the time necessary for the determination, and there is always a loss of 17-ketosteroid involved (sometimes as much as 10 to 15 per cent, 9). It is simpler to make a correction for the yellow colored fraction by determining the extinction coefficients for the reaction solution with a green and a blue filter and using the Gibson and Evelyn equation as outlined by Talbot (10).

The experimental tests presented show that more than 90 per cent of the hormone present in a urine sample is extracted and determined by the method outlined. When the normal variations in hormone excretion are considered it is evident that this degree of preciseness is sufficient for clinical diagnostic purposes. To illustrate the range of individual differences in 17 ketosteroid output reported in the literature the following values are listed. Fraser, *et al*, (2), list a range of 5.1 to 14.2 mg/24 hr with an average of 9.0 mg/24 hr, for normal females, and for males 8.1 to 22.6 mg/24 hr with an average of 13.8 mg/24 hr. In addition to this, they report a daily variation for individuals that may amount to as much as 5 mg. Werner (9) states that the daily variation observed in both males and females was within  $\pm 40$  per cent about the mean value. Talbot and Butler (11) declare that the chances are 2 to 1 that a single assay will fall within 15 per cent of the 17 ketosteroid value obtained by averaging 30 or 40 consecutive daily assays. The clinical conditions in which the test may

be of use result in values either significantly lower or very much higher than the normal. Fraser, *et al* (2), report values of 132 to 220 mg/24 hr for adrenal tumor cases. The same authors found less than 0.5 mg/24 hr for women with Addison's disease and 1.5 to 6.4 mg/24 hr (average 2.7 mg/24 hr) for men. Only 2 of 15 patients with panhypopituitarism showed any detectable 17 ketosteroids. Hypothyroid cases also were very low. It appears that an analysis must show a considerable deviation from the normal to be significant, therefore the preciseness of the determination is of relatively minor importance.

#### SUMMARY

A rapid method for the extraction and determination of total urinary 17 ketosteroids is presented. The urine is hydrolyzed with 10 per cent HCl, extracted for 10 minutes by refluxing with boiling  $\text{CCl}_4$ , and the hormone content determined by the alkaline m dinitrobenzene technique. Tests of the accuracy of the method show a maximum variation of about  $\pm 5$  per cent for any stage of the process, and an overall variation of  $\pm 10$  per cent or less. Since the individual and daily variations are considerably in excess of this amount the procedure is satisfactory for clinical use.

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# Purification of Equine Gonadotropin and Its Effect on the Appearance of Antigonadotropic Substances in Human Sera<sup>1,2</sup>

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THE PRESENCE of antigonadotropic substances in human sera following treatment with equine gonadotropin (pregnant mare serum) has been demonstrated in men and women (1, 2). Tests for the presence of these antigonadotropic substances in human sera indicated that they were initially present about 10 weeks after treatment was instituted and increased in titer with continued therapy. Furthermore, these antigonadotropic substances remained in the serum for months after cessation of treatment. Therefore, if the equine gonadotropic activity is nullified by the body as is indicated by our tests in mice and rats, then continued treatment with the hormone would be essentially valueless.

Whether the antigonadotropic evoking factor is the actual hormone or the non-hormonal material in the extract remains to be determined with crystalline preparations. However, extracts of different degrees of purity have been investigated and Gordon (3) has recently shown in tests in rabbits and rats, using 4 pregnant mare serum preparations of different degrees of purity, that the antiserum formed to the more purified equine gonadotropin was the more inhibitory. Gordon's results suggest that antihormone formation to

equine gonadotropin is evoked by the actual hormone or some chemically related substance. The present study was undertaken to determine whether further purification of equine gonadotropin would influence the appearance of antigonadotropic substances to equine gonadotropin in the human species.

Over a period of 18 months, 21 women, aged 17 to 40 years, were treated with equine gonadotropin. Of this group, 3 patients, aged 17 to 20 years, were suffering from primary amenorrhea whereas the other patients exhibited secondary amenorrhea or irregular menstrual periods for 8 months to 10 years. In addition, the evaluation of the patient's urinalysis, blood count, hemoglobin determination, basal metabolic rate and endometrial biopsy were made. In addition, a serum test for antigonadotropic substances against equine gonadotropin was obtained before the hormone was administered.

One male patient was treated for hypogonadism.

The patients received either of two preparations of equine gonadotropin,<sup>4</sup> one being approximately 2.5 times more highly purified than the other on the basis of total nitrogen. One lot (#18861) contained 0.004 mg. total nitrogen per 20 I.U. (one Cartland-Nelson rat unit) and 2 other lots (#18818, 19487) contained 0.0016 mg. total nitrogen per 20 I.U. The less purified preparation was commercially available and was used clinically.

<sup>4</sup> The equine gonadotropin, (Gonadogen) used in the studies was generously supplied by Dr. G. F. Cartland of the Upjohn Company, Kalamazoo, Mich. One Cartland-Nelson rat unit is the equivalent of 20 I.U.

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TABLE 1. ILLUSTRATION OF DATA OBTAINED IN TESTING FOR ANTIGONADOTROPIC SUBSTANCES TO EQUINE GONADOTROPIN IN HUMAN SERA FROM CASTS OF AMENORRHEA

Treatment	No. of Mice	Injections		Ovarian Weight, mg.	Uterine Weight, mg.	Neutralization
		Equine gonadotropin I.U.	Serum, cc.			
None	4	10	0.9	9.8	28.0	negative
Equine gonadotropin	4	10	0.9	5.2	37.0	partial
Equine gonadotropin	3	10	0.9	3.1	33.0	complete
Equine gonadotropin	3	10	0.9	2.5	5.3	complete
<i>Control experiments</i>						
None	152	10	none	9.4	30.7	
None	20	none	none	3.0	6.8	

Patients generally received 4 injections of hormone during the first 9 to 12 days of each month of treatment. Most of the cases were treated for 1 or 2 months, but in 3 cases they were treated for 3 months and 1 case was treated for 4 months. Total dosages of 800 to 1000 I.U. (40 to 450 Cartland-Nelson rat units) of equine gonadotropin were given, dosages of 1000 or 4000 I.U. being the usual amount administered during a single month. If as much as 2000 I.U. was given, the patient received at 3 to 3-day intervals subcutaneous injections of 100, 400 and 600 I.U. and a final injection of 100 I.U. intravenously.

The blood obtained for antigonadotropic tests was allowed to clot, the serum separated and centrifuged and stored in the refrigerator until tested, which was usually 24 to 48 hours after the blood sample was taken. As test animals, 22-day-old female mice were used. All test mice received a total of 10 I.U. of equine gonadotropin and, at a different site, a total of 0.9 cc. of the serum to be tested. Injections were made subcutaneously once daily for 3 days and the animals were killed 72 hours after the first injection. The weights of the ovaries and uteri were obtained, the latter after removal of intra-uterine fluid. At least 3 or 4 mice were used for each serum test and 2 or more mice receiving equine gonadotropin alone, served as controls. The patient's serum was tested against the lot of hormone with which the patient had been treated.

#### RESULTS

The sera of each of 39 patients were tested for antagonistic substances against equine gonadotropin from pregnant mare serum be-

fore hormone treatment was begun. The 21 patients later treated with the hormone are included in this group. In only one case was there a suggestion of partial inhibition of the gonadotropic action. In this case, the ovarian weight for 3 mice treated with equine gonadotropin and serum averaged 5.3 mg. whereas equine gonadotropin alone increased ovarian weight to 9.0 mg. in 2 control animals. However, this patient did not develop antigonadotropic substances when treated with equine gonadotropin. On the other hand, the serum from one patient appeared to augment the response to equine gonadotropin in 3 mice in which the ovarian weight averaged 14.2 mg. as compared with ovaries averaging 9.2 mg. from 2 mice injected with only equine gonadotropin. Considering the group as a whole, 100 mice received sera from 39 individuals plus equine gonadotropin and the ovarian weights averaged 8.9 mg. as compared with the ovarian weight of 9.2 mg. of 57 littermate mice injected with equine gonadotropin alone. It is evident that antagonistic substances to equine gonadotropin are not normally present in the human female.

Serum from the one male patient was negative prior to treatment.

The sera from 22 amenorrheic women obtained before treatment with equine gonadotropin were also tested. Mice were injected with a total of 0.9 cc. of serum alone and in 14 cases no stimulation was obtained, the ovarian weight and uterine weights being 2.5 and 8.0 mg., respectively, which compares with the organ weights of uninjected mice (table 1). The sera from 8 amenorrheic patients caused a definite stimulation of the uteri of the test

mice which averaged 31.4 mg. (20-50 mg., range). The ovaries were not stimulated, weighing 3.2 mg. As little as 0.3 cc. of serum from one patient increased uterine weight to 31.9 mg. Unfortunately, only 2 of these 8 women returned to the clinic. Retests were made in these 2 cases and the serum (alone) was tested in normal and spayed mice but negative results were obtained. The reason for this phenomenon is not clear with the evidence at hand.

The presence of antagonodotropic substances can be determined by a partial or complete suppression of the ovarian weight increase usually produced by a uniform dosage of equine gonadotropin. The antagonistic effect may reach a sufficiently high titer to cause an inhibition of both ovarian and uterine weight increases. An example of these data is shown in table 1. The administration of 10 I.U. of equine gonadotropin increased ovarian weight to the same degree as 5 Cole-Saunders rat units (10 I.U.), the results with the latter amount were given in a previous report (1).

Seven patients were treated with 1200 to 9000 I.U. of preparation #18861, which contained 0.004 mg. total nitrogen per 20 I.U. In

6 patients antagonodotropic substances were first definitely present in the sera 36 to 42 days after the initial injection (av. 63 days). Two additional patients were injected with this preparation but could be studied for only 28 and 42 days after treatment at which time the sera were negative; on the average, there was not sufficient time for the development of antagonodotropins to equine gonadotropin.

Sera tests were made prior to the appearance of antagonists in all but one case (E.O.) at several intervals after they appeared. Table 2 illustrates the time in days after the first injection when the sera tests were made and also the approximate time of administration of additional equine gonadotropin. At 9 months after the start of the injections, the serum of one patient (E.S.) remained strongly inhibited whereas with 4 patients it was possible to determine the approximate time of disappearance of the antagonodotropic substances. These data suggest a period of 3 months after the last injection as the minimum time required for the loss of demonstrable antagonistic substances.

A detailed illustration of the test data obtained from one patient (P.C.) is shown in table 3. The serum from this individual contained

TABLE 2. ANTIGONADOTROPIC ACTIVITY OF SERA FROM PATIENTS FOLLOWING TREATMENT WITH THE LESS PURIFIED EQUINE GONADOTROPIN (#18861)

Patient, Age	Sera Tests, Days after First Injection Equine Gonadotropin, I.U.									
E.S., 36	0	24	44	66	165	245	270			
	2000	4000		+	2000	+	+			
P.C., 26	0	28	48	63	78	112	125	170	191	247
	4000		2000	+	+	+	+	+		
N.W., 28	0	28	63	84	286					
	4000		4000	+	+					
B.P., 40	0	47	75	145	167	244				
	4000		1000	+	+					
F.C., 24	0	70	92	185						
	2000		+							
E.O., 27	0	36	70							
	2000	+	+							
A.D., 28	0	42	186	214	256					
	1200									

+ =antigonadotropic substances present.

lately inhibited the ovarian stimulating effect of equine gonadotropin in 6 tests made during a period of 4 months, but at no time was the serum strong enough to inhibit uterine weight increase. It was interesting to us to find that tests for antigonadotropins did not remain positive for a longer period of time in this patient in view of the fact that a third series of injections was given at 91 to 105 days after the first injection. Varied amounts of serum obtained at 78 days after the start of treatment were tested in combination with the uniform dose of equine gonadotropin, the results of which are shown in table 4.

The male patient received equine gonadotropin (#18861) and antigonadotropin substances were observed at 61 days after the initial injection.

The only patient that failed to exhibit antiody formation with the less purified preparation was one to whom the smallest dosage had been administered (1200 IU). However, it will be noted in table 2 that we were not able to obtain serum at the more critical period between 42 and 186 days so that it is possible that antihormones could have been detected during this time since the 60 to 70 day period appears to be the more likely time to find first the presence of antagonistic substances.

The more highly purified equine gonadotropin preparations (#18818, 19487) were administered to 12 individuals in total dosages of 200 to 8000 IU. Patients were injected with these amounts to permit direct comparison

TABLE 4 ANTIGONADOTROPIC ACTION OF VARIOUS AMOUNTS OF SERUM

No of Days Treated	No of Test Mice	Total Dosage		Average Ovarian Weight mg	Average Uterine Weight mg
		1 g gonad IU	Serum cc		
<i>Patient P C preparation #18861 administered</i>					
78	3	10	0.9	3.9	34.0
	3	10	0.6	4.5	42.0
	3	10	0.3	6.7	37.0
	3	10	0	10.8	38.0
<i>Patient M W preparation #18818 administered</i>					
49	3	10	0.9	2.5	5.3
	3	10	0.3	2.4	6.8
	3	10	0	7.3	34.0
Control tests	20	0	0	3.0	6.8

with the effects of the less purified preparation. As shown in table 5, only one (M W) of the 12 individuals developed antigonadotropic substances in the sera, although 7 women were injected with the 8000 IU dosage. In virtually all of these cases, sera tests were made during what might be the anticipated time for antigonadotropic substances to make their appearance. However, it must be pointed out that the one positive case in this series had a serum with the highest antihormone titer of any obtained. The serum (0.3 cc) not only abolished the increase anticipated in ovarian weight in the test mice but in the uterine weight as well (table 4).

The data obtained on one case (E M L) treated with the more purified preparation of equine gonadotropin are shown in table 6. The absence of any antagonistic substances in the serum of this patient is well illustrated by the very similar ovarian weights of the test mice as compared with the littermate control mice injected at the same time with equine gonadotropin alone.

#### DISCUSSION

The results in the present investigation are in agreement with previously reported results (1, 2) that antigonadotropic substances will develop in the blood of human beings following treatment with equine gonadotropin from pregnant mare's serum but our data show that with highly purified preparations the incidence is markedly reduced. The antagonistic sub-

TABLE 5 SERA TESTS IN MICE OF ONE PATIENT (P C) TREATED WITH THE LESS PURIFIED EQUINE GONADOTROPIN (#18861)

IU Injected	Time After Initial Injection days	Average Ovarian Weight mg		Test
		Equine gonadotropin and serum	Equine gonadotropin only	
4000 (1-10)	0	10.2	8.0	—
	28	7.4	9.8	—
2000 (32-42)	48	3.1	9.1	+
	63	3.7	12.6	+
2000 (91-105)	78	3.9	10.8	+
	112	2.6	9.8	+
	125	2.7	8.8	+
	170	4.7	8.1	+
	191	11.8	11.5	—
	247	12.0	9.2	—

TABLE 5. ANTIGONADOTROPIC ACTIVITY OF SERA FROM PATIENTS FOLLOWING TREATMENT WITH THE MORE HIGHLY PURIFIED EQUINE GONADOTROPIN (#19487, 18818)

Patient, Age	Sera Tests, Days after First Injection Equine Gonadotropin, i.u.							
M.G., 36	0 4000	29	42 4000	56	157	199		
M.W., 17	0 4000	31	58 4000	75				
E.M.L., 20	0 4000	31	65 800	3200	79	117	145	201 216
M.S., 17	0 4000	29	56 4000	63				
M.F., 25	0 2000	28	63	84	99			
E.C., 24	0 800	52 400	126 800	175				
L.M.T., 19	0 1200	63	77					
E.L., 34	0 4000	28	63 4000	286				
L.L., 23	0 4000	42 4000	245					
M.W., 18	0 4000	28	42 +	49 +	61 +			
M.G., 34	0 4000	45	57	79	99 800	249	263	
I.P., 23	0 2000	65	93 800	114				

+ = antigonadotropic substance present.

tances may first appear as early as 36 days after the initial injection when as little as 100 R.U. (2000 I.U.) of equine gonadotropin have been administered. A 9- or 10-week period is the more usual time for the initial indication of antigonadotropins, and this time-period cor-

TABLE 6. SERA TESTS IN MICE ON ONE PATIENT (E.M.L.) TREATED WITH THE MORE HIGHLY PURIFIED EQUINE GONADOTROPIN (#19487)

I.U. Injected days	Time After Initial Injection, days	Average Ovarian Weight, mg.		Test
		Equine gonado- tropin, sera	Equine gonado- tropin	
4000 (1-10)	0 31	7.1 6.2	7.7 7.8	— —
4000 (35-59)	65 79 117 145 201 216	8.0 9.6 9.0 11.8 8.0 6.7	8.4 9.9 8.6 11.8 8.2 6.3	— — — — — —

responds with data obtained from patients treated with another equine gonadotropin preparation (1). Strongly inhibitory serum was obtained for as long as 9 months after the initial injection of equine gonadotropin, the antigonadotropins being present during the last 7 months of this period. After cessation of treatment, a period of at least 3 months is required for the antigonadotropic substances to disappear. One patient treated with equine gonadotropin developed an extremely high titer of antigonadotropins and the serum was tested 4 and 8 months after the last injection. Complete absence of antagonistic substances was evident at 8 months (4).

Pregnant mare serum extract,<sup>4</sup> containing 0.004 mg. of total nitrogen per 20 I.U. developed antibodies in 6 of 7 patients but another preparation, 2.5 times more purified (0.0016 mg. of total nitrogen per 20 I.U.), and used in the same dosage, resulted in antigonadotropin

formation in only one of 12 patients. These data suggest that the antigonadotropic substance is not evoked by the hormone itself, in contrast with the experiments on animals reported by Gordon (3).

Considerable information on this antihormone problem has been reported and the reader is referred to excellent review articles in the subject (5, 6). However, it should be pointed out that comparisons of crude and highly purified preparations of equine gonadotropin as to their ability to develop antihormones have been made in rats, rabbits and monkeys (3, 7, 8). These investigators found the highly purified preparations capable of developing antihormones and, indeed, Gordon's results (3) show that the antagonistic reaction is more intense when sera from animals treated with the highly purified material is used. One can not explain these differences in results by direct comparison because of the difference in species, dosage and equine gonadotropin used. However, the species difference is readily evident and is further exemplified by the recent report of Smith (9) who showed in hypophysectomized monkeys that antibodies to equine gonadotropin are well developed in 20 to 25 days and these substances persist at very high titers for at least 7 months. On the other hand, Jailer and Leatham (1) obtained only a mildly inhibitory serum from patients treated with the same equine gonadotropin when tested 70 days after the start of treatment.

Our results indicate that increased purity of equine gonadotropin will markedly lower the tendency for antigonadotropin formation in the human being, and thus permit the use of larger doses and/or longer periods of therapy in cases in which it is necessary.

The presence of antigonadotropic substances in the blood of normal patients has been reported (10, 11) whereas Zondek and Sulman failed to find antagonistic substances to human chorionic gonadotropin in either normal or amenorrheic women (12). In human sera, Fellows (13) failed to find antigonadotropins or antagonistic substances to gonadotropins from human pituitaries. We tested the sera of 39 amenorrheic women for antigonadotropins

of equine gonadotropin and obtained only a suggestion of inhibition in one case. On treatment, this patient did not demonstrate antibody formation. We did find that sera from some patients would increase the uterine weight of test mice.

#### SUMMARY

Female patients suffering from amenorrhea were treated with either of two preparations of equine gonadotropin derived from pregnant mare serum, one being 2.5 times more highly purified than the other on the basis of their nitrogen content. Six of 7 patients injected with the less purified preparation developed antigonadotropic substances to equine gonadotropin in their blood. This was usually first evident in 9 to 10 weeks after the initial injection and persisted for at least 3 months after cessation of treatment, thus rendering equine gonadotropin therapy essentially valueless. However, with the more highly purified preparation only 1 of 12 patients developed an antigonadotropic serum. These results indicate that increased purification of the equine gonadotropin will markedly lower the tendency for the formation of antigonadotropins in the human.

The sera of 39 amenorrheic women tested prior to hormone therapy showed that antigonadotropins of equine gonadotropin are normally absent.

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# A Case of Cushing's Syndrome with Adrenal Cortical Hyperplasia, without Pituitary Basophilic Adenoma or Hyperplasia

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THE CASE reported in this paper has been the subject of two previous reports (1, 2). It seems desirable to conclude the case now in this final paper because the patient had been under observation for a period of 8 years and the diagnosis has been verified by autopsy.

## CASE REPORT

The important features, as published in the two previous reports (1, 2) are as follows: *E.R.*, a white unmarried female was first seen at Jefferson Hospital in April, 1934. Irregularity of menses appeared in 1933. The weight had increased, she had noticed growth of hair in her face, dryness of the skin, marked redness of the face, polydipsia, occasional swelling of ankles, defluvium of the hair of the scalp. She presented a typical appearance of Cushing's syndrome with adiposity of the trunk, moon face, ruddy skin, hirsutism and acne. The blood pressure was normal at that time and the glucose tolerance curve was of the diabetic type. No decalcification of the bones was detectable. The sella turcica showed some ballooning in the roentgenogram and the posterior clinoids appeared thinned. In January, 1935, an intravenous pyelogram failed to reveal signs of an adrenal tumor. In October, 1936, she was studied in New Haven Hospital by Dr. Harvey Cushing and was listed by him as a basophilism suspect. A periadrenal air insufflation showed no adrenal tumor.

The patient was treated in the period between 1934 and 1937 with deep irradiation of the pituitary. Following this treatment in June, 1936, the plethoric appearance and the acne of the face disappeared, hirsutism regressed markedly and the patient lost 13 pounds. In October, 1936, she had a menstrual period. Improvement lasted for about one year. When seen in February, 1938, all of the previous signs and symptoms had recurred. Subsequent pituitary irradiation

was without effect. In 1939 the disease had progressed further. Blood pressure had risen to 160/120 mm.Hg. The heart was enlarged. In September 1940, she had become progressively weak, the blood pressure was 200/160 mm. Hg and frank diabetes was present. At this time periadrenal air insufflation was performed by Dr. Kenneth Fry and the roentgenogram revealed both adrenals to be enlarged. No tumor could be outlined. In November, 1940, treatment with diethylstilbestrol was started, the dosage being 1 and later 2 mg per day. This was followed by marked improvement. In spite of continued treatment with diethylstilbestrol this improvement lasted only about 4 months. In February, 1941, diabetes recurred, hirsutism increased, the blood pressure was 160/100 mm.Hg and she again became very weak.

In March, 1941, at the time of the last report (2) she was still in the hospital. The insulin requirement was now 30 U of protamine zinc insulin with a diet of 2000 cal., 70 gm. of protein and 165 gm. of carbohydrate. When she left the hospital in June, 1941, cardiac decompensation had subsided under bedrest and treatment with digitalis and the blood pressure was 175/120 mm.Hg. The diabetes was controlled as outlined above. She was instructed to continue on this regime and to continue taking 2 mg. of diethylstilbestrol daily. She did this under supervision of her family physician. She was seen at regular intervals in the Endocrine Clinic. However, there was no improvement of her condition. In the course of the next months she began complaining of back pain of increasing severity. The ankles started swelling again.

She was readmitted to the hospital on Jan. 6, 1942. The weight loss was now very marked (107 pounds). Edema of the lower extremities was extensive. Blood pressure was 210/170 mm.Hg. Fifty-six to 64 U of regular insulin controlled the diabetes on a diet of 2000 cal., 180 gm. of carbohydrate, and 70 of protein.

Demineralization of the bones had progressed since the time of the last examination (2). Roentgen-ray examination of the spine showed a marked degree of collapse of the seventh, definite narrowing of the dis-

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enth and twelfth thoracic vertebrae, marked collapse of the first and beginning collapse of the third and fourth and possibly of the fifth lumbar vertebra. All of these vertebrae as well as the sacrum showed evidence of osteoporosis.

The skull again showed demineralization of the bones, having a somewhat mottled appearance. The sella turcica did not appear to have changed in size or appearance since the time of previous examination in 1940. Serum calcium was 10.6 mg. per cent, phosphorus 3.3 mg. per cent, phosphatase 21.7 Bodansky units. She was given a diet low in calcium for a 3-day test period. The calcium intake for this period was 330 mg. The urinary calcium excretion was 500.7 mg. in the 3 days. During this test period 17.93 gm. of N was excreted in the urine. The N intake was 31.8 gm. No attempt was made to determine the N excretion in the feces.

She continued taking 2 mg. of stilbestrol daily. On Jan. 25, 1942, treatment with testosterone propionate, 25 mg. 3 times weekly by intramuscular injection was started.

Her condition deteriorated rapidly. Several teeth became loose and fell out. She developed an infection of the right ear and several purulent lesions on the face. Bacteriologic culture revealed streptococcus hemolyticus. The temperature rose to 101°F. In spite of treatment with sulfadiazine the infection progressed, cellulitis developed and on January 25 crabs of the face was noted. The temperature rose to 102°F. She died on Feb. 25, 1942.

#### AUTOPSY REPORT

The general external development has been adequately considered above and the description need not be repeated here. Evidence of a rather marked loss in weight, however, was exhibited by the presence of many abdominal striae and the paucity of subcutaneous tissue of the extremities. The right side of the face and the neck showed an extensive purulent cellulitis which had been previously drained by two surgical incisions.

The heart was slightly enlarged, weighing 420 gm. The left ventricle measured 1.8 cm. in thickness and the right 0.6 cm. The aorta showed minimal atherosclerosis. The lungs, other than manifesting some congestion and edema, revealed no gross pathologic changes. The spleen, liver, kidneys and gastro-intestinal tract were essentially normal.

A careful search in the anterior mediastinum failed to reveal any thymic tissue. The thyroid was well encapsulated and on section disclosed no foci. Only two parathyroid glands could be identified. One measured 3 and the other 2 mm. in diameter. The pancreas was not enlarged. Multiple transverse sections, each about 3 mm. in thickness, disclosed several minute hemorrhagic and necrotic foci. The ovaries were flat and atrophic measuring 2 cm. in diameter and 0.6 cm. in thickness. Each contained several white bodies but no corpora lutea. The fallopian tubes were normal. The uterus was not enlarged. Its cavity was of normal

shape and size. The endometrium was pink and scanty. The cervix and vagina showed no gross pathologic changes.

Of the skeletal system only the skull, ribs and vertebrae could be examined. The cranium was quite thin and the bones were more brittle than usual. The pituitary gland measured 0.7 cm. superiorly-inferiorly and 2.0 cm. transversely. The inner surface of the pituitary fossa was smooth and glistening. It showed no evidence of erosion. The cortex of both the ribs and the vertebral bodies was thin and brittle. The marrow was friable. The third lumbar vertebra contained a compressed transverse fracture.

The adrenals were markedly enlarged. Each weighed 30 gm. The right adrenal measured 9×6.5×1.5 cm. and the left measured 8×4.5×1.5 cm. The consistency was firm but lacked the hardness of cancerous tissue. Cut surfaces showed a uniform hyperplasia of the cortices. They were orange-yellow, sharply demarcated from the medulla and exhibited no necrotic or hemorrhagic foci. Each adrenal, in addition, contained several small circumscribed, peripheral adenomas measuring up to 0.6 cm. in diameter. These were similar in all aspects to the main cortical tissue.

*Microscopic examination.* Serial sections of the hypophysis revealed no basophilic adenoma. The cytoplasm of most of the basophilic cells, and of an occasional eosinophilic cell, contained small refractile, sharply defined droplets, some of which possessed granular debris. They were arranged either singly or in clusters and appeared to concentrate around, and sometimes to involve, the nucleus.

Sections of the leptomeninges and the cortices disclosed a diffuse, purulent meningitis with focal areas of metastatic encephalitis.<sup>2</sup>

The normal architecture of the cortex of the adrenals was well preserved. The capsule was of normal thickness and composed of dense fibrous tissue. The immediately subjacent zona glomerulosa was well defined. The cells were arranged in irregular groups and were relatively small. Their cytoplasm was homogeneous and stained a deep pink color. The nuclei were round, vesicular, uniform and for the most part centrally placed. Often two were found within a single cell. The intervening capillaries were filled with blood and were quite conspicuous. The zona fasciculata was exceptionally well preserved. The columns of cells were arranged in a straight radial pattern between which were slender thick and thin walled capillaries. The cells were much larger than those of the zona glomerulosa. The cytoplasm was pink and foamy or vacuolated. Vacuolated cells were particularly abundant in the midportions of the columns. The nuclei were similar to those of the zona glomerulosa zone. They were either centrally placed, or, in the vacuo-

<sup>2</sup> We are indebted to Dr. B. Alpers for the histologic examination of the pituitary gland and the brain.

Dr. L. Eisenhardt of Yale University School of Medicine examined slides of the pituitary gland and found the basophilic cells to show pronounced Crooke changes. We are grateful for her permission to quote this from a personal communication.

lated cells, pushed aside. The zona reticularis was less well defined. The cells were irregularly arranged and some of these were large pale cells, others were smaller and dark. The former resembled the foamy cells of the zona fasciculata while the latter resembled the cells of the zona glomerulosa. In addition, many of the small cells contained in their cytoplasm a sprinkling of fine brown, dust-like granules. The surrounding capillary spaces were quite prominent and filled with blood. The medulla showed no histopathologic changes.

The adenomatous nodules were essentially similar, with the exception that the different zones, although easily recognizable, were less prominent than in those of the adrenal proper.

Sections of the adrenals stained with ponceau-fuchsin as outlined by Uotila (3) were positive for fuchsinophilic granules.

Sections of the pancreas stained with hematoxylin and eosin showed no changes in the islets of Langerhans. Special stains for  $\alpha$  and  $\beta$  cells could not be done since the body was autopsied 6 hours after death. The exocrine portion of the pancreas, however, revealed numerous small and large areas of recent necrosis and hemorrhagic extravasation. Acute inflammatory reaction surrounding these foci was minimal. The smaller vessels showed extensive arteriolar sclerosis with occasional complete obliteration of the vascular lumen. In addition to this, several vessels were plugged with antemortem thrombi. The vascular changes in the kidneys were of a similar nature although less severe. There were, in addition, focal areas of arteriolar and glomerular necrosis. The cortices contained several scars and the interstitial tissue showed some edema.

Sections of the vertebral bodies showed atrophic bony spicules with severe hypoplasia of the marrow cells. The parathyroid glands showed a slight fatty infiltration but no histopathologic changes. The ovaries contained a few large follicles and old and young corpora albicantes but no corpora hemorrhagica. The endometrium was of the interval type. The vaginal mucosa was not atrophied. Its superficial cells showed some keratinization while the prickle cells exhibited vacuolar degeneration. Sections from the remaining organs revealed no contributory findings.

*Comment.* Adrenal glands from several fetuses between 3 and 4 months gestation, from a child 12 years old, from an adult human female and from several adult rats, both normal and castrated, were used as controls for the ponceau-fuchsin stain. The results were so inconsistent that, although fuchsinophilic granules were present in the adrenals of the case under discussion, it could not be stated unequivocally that the cells taking the stain were 'androgenic' cells.

The metastatic encephalitis, the recent vascular thrombi with resulting pancreatic necrosis and the focal arteriolar and glomerular

necrosis of the kidneys, probably originated in the acute cellulitis of the right side of the face and neck.

## DISCUSSION

This case presented Cushing's syndrome with all its classic features. Autopsy revealed neither tumor of the pituitary gland, nor diffuse hyperplasia of basophil cells, nor tumor of any other gland save several 'knoten' of the adrenal cortex. The measurements of the pituitary gland were slightly above the normal average. There was a marked bilateral cortical hyperplasia of the adrenal which had several small adenomata.

Adrenal cortical hyperplasia is a frequent although not constant finding in cases of Cushing's syndrome due to pituitary basophilism. Eisenhart and Thompson (4) reviewed 67 cases of Cushing's syndrome with pituitary changes and noted adrenal cortical hyperplasia in 42 cases. On the other hand, adrenal cortical hyperplasia in the absence of pituitary basophilism has been found in several instances: (5-8).

*Crooke-changes of the basophilic cells.* Crooke (9) examined the pituitary glands of 12 cases of Cushing's syndrome. Six of these had basophilic adenoma of the pituitary gland. In the other 6 cases no basophilism was found. 3 showing adrenal cortical changes and 3 showing tumors of the thymus. In all cases 'hyalinization' of the basophilic cells of the pituitary gland was found. Eisenhart and Thompson (4) found hyalinization in 40 cases of basophilic adenoma in those basophilic cells which did not constitute the adenoma. There was hyalinization of the basophiles in this case. Crooke considered this change as the causative lesion of the syndrome. Severinghaus and Thompson (10) interpret the hyalinization as a degenerative change following a period of physiologic overactivity. This latter interpretation may be tentatively supported by observations in our case.

*Gonadotropic hormone.* In an early period of the disease there was a marked increase of gonadotropic hormone in urine and serum on several occasions (2). The first assay report in 1934 reads 'not increased.' This assay was not performed by us and the result reported may

be explained by the inaccurate methods of assay available at that time. Later assay values were always low (table 2, reference 2). This would tend to indicate that there was a period of overactivity of the pituitary gland followed by decreased function.

*Adrenocorticotrophic hormone.* The assays of adrenocorticotrophic hormone show the same tendency, increased values followed by a decrease. We should, however, like to make some reservations in quoting these results. Most of the assays were made with serum using the method of Jores (11). For reasons discussed elsewhere (12), we do not consider this method reliable and have abandoned its use entirely. However, the assays did reveal decreasing adrenocorticotrophic activity of the serum (2). Assays of adrenocorticotrophic hormone in the urine by the method described elsewhere (12) were performed in April, 1941, and again in 1942. Neither urine sample showed adrenocorticotrophic activity at this late stage of the disease.

The results of the assays of gonadotropic hormone and, with reservations, also those of adrenocorticotrophic hormone, might be interpreted as early hyperpituitarism with subsequent lowering of pituitary function, possibly due to exhaustion of the gland. Some clinical observations in this case would tend further to support such interpretation. The patient improved greatly after deep roentgen-ray irradiation of the pituitary (1). Whether this was a true therapeutic effect or a spontaneous remission coincident with treatment given at that time cannot, of course, be definitely stated. Spontaneous remissions are rare in this disease.

Later, after the relapse in 1938, further irradiation of the pituitary gland was ineffective. It does seem possible that by this time the adrenal glands, hyperplastic through stimulation from the pituitary gland, had become independent of the 'master gland' and that at about this time a primary hyperpituitarism had developed into a hypercorticalism. The latter would have been secondary and dependent on the pituitary stimulation at first.

*Periadrenal air insufflation.* In view of the possible sequence of events just described, it would be of interest to know at what time in

the course of this patient's disease the adrenals had become markedly hyperplastic. Unfortunately, no definite answer to this question is available. Periadrenal air insufflation was performed twice at New Haven Hospital, in 1936 and 1938. No obvious unilateral enlargement of the adrenal glands was found, and on account of the patient's adiposity no definite estimate of the size of the adrenals was possible.<sup>3</sup> In 1940 periadrenal air insufflation was performed at Jefferson Hospital. Again the absence of adrenal tumors was stated, but both adrenals were definitely enlarged.

*Androgen excretion.* The androgen excretion in this case was high and dropped to normal values under treatment with diethylstilbestrol. At first (1940-1941) this decrease in androgen excretion coincided with considerable clinical improvement. However, there was a recurrence of symptoms in February, 1941, as described in our previous communication (2). Urinary androgen assay on May 26, 1941, showed 12 i.u. per 24 hours. No further assays were performed during the next months until her return to the hospital in January, 1942. At this time (January, 1942) the 17-ketosteroid excretion was 31 mg. per 24 hours. No bioassay of androgens was performed at that time. Although no previous determinations of 17-ketosteroids had been made, the value obtained is undoubtedly high. To our knowledge no extensive comparative study of androgen bioassay and 17-ketosteroid determination has been published. This 17-ketosteroid value cannot, therefore, be compared with the previous bioassays for androgenic material.

There remains, however, the fact that the androgen excretion decreased during treatment with diethylstilbestrol. The possibility that a decrease of androgen excretion was purely coincidental and not related to the treatment seems improbable, particularly because a decrease in androgen excretion under treatment with diethylstilbestrol was observed by us in a second case (2).

No explanation can be given for the fact that ultimately the diabetes and the osteoporosis progressed in spite of continued treatment with

<sup>3</sup> We are greatly indebted to Dr. K. W. Thompson of Yale University School of Medicine for this information on his findings.

diethylstilbestrol, while at the same time the androgen excretion remained at a low level. It might be possible that stilbestrol was more potent in its suppression of androgen excretion than on excretion of other cortical steroids. This explanation would assume an at least temporary dissociation of production and excretion of various cortical steroids. Seventeen-ketosteroid excretion was high at a very late stage of the disease, but unfortunately we have no bioassay of androgens of this time. It might be mentioned that at autopsy only small amounts of fuchsinophile 'androgenic' cells (3, 13) were found in the adrenals. The staining reaction did not differ from that in some of the normal control specimens and was very much less extensive than was found by Broster and Vines (13) and others. The low androgen excretion during the last year of the patient's life would be in keeping with the histologic findings. However, the significance and specificity of the staining reaction is still open to much doubt and we therefore cannot attach importance to it.

*Pregnandiol excretion.* As mentioned in our previous report, this patient excreted 8 mg. of pregnandiol per 24 hours in September, 1940, despite amenorrhea. Under treatment with diethylstilbestrol the excretion dropped to 6 mg. in January, 1941 (2). Under continued treatment with diethylstilbestrol the excretion decreased further to 3 mg. (June, 1941) and 2 mg. (January, 1942). It will be noted that the decrease of pregnandiol excretion continued to quite low values at a time of recurrence of symptoms.

Excretion of pregnandiol in absence of a corpus luteum is considered to be due to progesterone production by the adrenal cortex. Excretion of large amounts of pregnandiol in cases of virilism has been reported (14, 15, 16). Talbot, *et al.* (17), found the excretion of pregnandiol increased in some cases of adrenal cortical hyperplasia and normal in others.

*Demineralization and calcium metabolism.* Osteoporosis was not an early event in the course of the disease in this patient. None was found from 1934 to 1937. Some demineralization of the spine was first noted when the patient was in New Haven Hospital in 1938, and again when she was in Jefferson Hospital

in 1939. It progressed very rapidly during the patient's last year of life. The progression of the demineralization was most marked at the time when the excretion of androgenic hormones and of pregnandiol was decreasing. Whether the treatment with diethylstilbestrol during this time failed to arrest the demineralization or actually increased it cannot be decided.

In January, 1942, a calcium balance study was performed using the dietary regime of Bauer and Aub (18). At this time demineralization was far progressed and had led to collapse of several vertebrae. The excretion of 500.7 mg. of calcium in the urine during a 3-day period as against an intake of 330 mg., indicated a negative calcium balance. Similar observations in patients with Cushing's syndrome have been published (19, 20). The serum calcium level at this time was 10.6 mg. per 100 cc. The phosphorus was 3.3 mg. per 100 cc. and phosphatase 21.7 Bodansky units. While Ca and P values were normal even at this period, the high phosphatase values indicate a reparatory tendency of the organism. Phosphatase levels have been determined in this patient in November 1939 (3 Bodansky U), and in October, 1941 (8.8 Bodansky U). Some demineralization had been observed at the time these values were established. Only when the demineralization had progressed to extreme degrees was the serum phosphatase significantly elevated.

*Nitrogen balance.* Albright, *et al.*, have suggested that in Cushing's syndrome a number of symptoms, including the osteoporosis, is due to disturbed protein metabolism. A slightly negative nitrogen balance was found and considered to be due to increased gluconeogenesis (19). In our patient a nitrogen balance study was performed in January, 1942. At this time the osteoporosis was extreme, the calcium balance negative and the diabetes marked. She had been treated with diethylstilbestrol for about a year and a half. In a 3-day observation period the N intake was 31.8 gm., the urinary output, 17.9 gm. The balance study is incomplete inasmuch as the N loss through the feces was not determined, but the values obtained do not seem to indicate a negative nitrogen balance.

Albright, *et al.* (19), have described a beneficial effect of treatment with testosterone

propionate in cases of Cushing's syndrome. The osteoporosis was improved and the negative calcium and nitrogen balance reverted to normal. Our patient received testosterone propionate for 2 weeks just prior to her death. At that time she had developed multiple purulent skin lesions, complicated by erysipelas. The failure to respond to testosterone under these conditions was to be expected.

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# Contribution to the Treatment of Essential Pruritus and Kraurosis Vulvae

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THE HORMONAL treatment of essential pruritus, kraurosis and leukoplakia of the vulva gives a more favorable prospect for alleviating the symptoms and curing the conditions than any known form of therapy. Roentgen-ray therapy in a series of 22 patients with such degenerative disorders resulted in cure in 27 per cent and temporary relief in 23 per cent of the patients, the remaining 50 per cent being refractory to treatment. Estrogenic therapy in a group of 38 patients suffering from pruritus vulvae resulted in cure in 66 per cent of the cases (4).

The local use of an ointment containing estrogen was instituted because it appeared that, when injected, only a fraction of the follicular hormone is utilized by the affected vulval tissues and the prolonged parenteral treatment and high dosage was unnecessary. This mode of topical medication was started independent of Zondek's (10) studies along the same lines and at about the same time. Ten patients of our series were treated by local inunction only. This resulted in complete cure in 6 cases and proved the effectiveness of directly applying the hormone to the affected tissues. Later, however, therapy involving the simultaneous local and parenteral administration of the estrogenic substance was instituted according to the following scheme. Four gm. of a salve containing estrogen equivalent in activity to 4000 I.U. of estrone was applied to the vulva by daily inunction for the first week. This was supplemented by injections of estradiol benzoate, 30,000 international benzoate units each, given every other day. During the second week the parenteral dosage was continued whereas the ointment (4000 I.U.) was employed on the days when injections were not given. During the third week local medication

was applied 2 to 3 times, according to the severity of the condition, and the parenteral dosage was decreased to 20,000 I.B.U. given twice each week. During the fourth and fifth weeks there were 1 to 2 local treatments per week supplemented by 2 injections of 10,000 I.B.U. of estradiol benzoate each. Beginning the sixth week, only percutaneous therapy was employed; 4000 I.U. were applied every 3 to 4 days. The whole course of therapy was continued over a total of 8 to 12 weeks. This, however, was not regarded as an inflexible regimen and the dosage largely depended upon the severity and responsiveness of the case. Later, other reports of gratifying results with local administration of estrogenic ointment in degenerative genital disorders of this type appeared (1, 2, 3, 5-9). Reifferscheid (7), following our procedure in a series of pruritus cases produced complete relief from symptoms in about 71 per cent of the patients.

## *Present Material, Therapy Employed and Results*

The present series of 68 cases of degenerative disorders of the outer genitalia consisted of 54 of pruritus vulvae, 6 of primary kraurosis and 8 of leukoplakic vulvitis and secondary kraurosis. There was no leukorrhea in these patients and there were no clinical manifestations of vitamin deficiency. The urine in all cases contained no sugar and the blood-sugar level was within normal range. A routine search for monilia and trichomonas vaginalis ruled out these parasites as causative factors of the pruritus.

As can be seen in table 1, two-thirds of the patients were women in the menopause. Among the women in the twenties and thirties, there were 2 patients with primary kraurosis and 1 with leukoplakia. Careful examination of

shown them to be in perfect health with apparently normal ovarian function. There was an unusual case of a 6-year-old girl with leukoplakia vulvae and subsequent kraurotic changes.

The therapy employed generally followed the same pattern as that outlined in connection with the previous series, but more emphasis was placed upon local treatment. Thus, with

ment was applied morning and night on days when injections were not given. Eight weeks after the initiation of local therapy, the parenteral dosage was decreased to 10,000 R.U. a week, the topical medication being continued at the same dosage. The whole course of therapy required 12 weeks. By decreasing the dosage of the parenterally administered hormone, as compared with our previous scheme,

TABLE 1. RESULTS OF ESTROGENIC THERAPY IN VULVAL DISORDERS

Age Group	Diagnosis and Result of Therapy				
	No. of patients	Pruritus vulvae	No. of patients	Primary kraurosis	No. of patients Leukoplakic vulvitis and secondary kraurosis
Prepuberal	0		0		1 cured
Reproductive age Apparently normal ovarian function	9	3 cured 2 improved 4 refractory	2	2 refractory	3 refractory
Hypo-ovarian function	7	4 cured 3 improved	0		0
Menopausal	38	24 cured 4 improved 10 refractory	4	2 cured 1 improved 1 refractory	4 2 cured 2 improved

variations as necessitated by both the clinical picture presented by the patient and her response to therapy, the following scheme was applied. During the first 1 to 3 weeks local treatment only was given. This consisted of vulval inunction with a salve, each dose representing the equivalent of 2000 and 5000 I.U. of estrone,<sup>1</sup> depending on the severity of the condition the lower or higher concentration was used. The ointment was administered twice a day. The skin was thoroughly cleansed prior to treatment. A cotton pad soaked with warm water was applied to the area for 5 minutes in order to facilitate absorption. The ointment was rubbed gently into the affected area until it disappeared. In the second, third or fourth week, particularly in those instances exhibiting hypoövarianism aside from the vulval changes, parenteral therapy was instituted consisting of two injections of 10,000 R.U. of estradiol benzoate<sup>1</sup> per week. The oint-

side effects of vaginal bleeding and discharge were mostly eliminated in the present series. However, parenteral hormone administration was not completely discontinued because it favorably influences the general condition of the patient and the systemic manifestations of the menopause.

Table 1 shows the results of the present scheme of treatment, which are slightly less favorable in the pruritus group of this series (57 per cent cured) than in our first series (4). This may be attributed to the fact that this series included patients with only the most severe conditions which had not responded to any kind of therapy previously, including roentgen-ray. Of a total of 54 cases, 74 per cent were permanently cured or markedly improved.

The respective groups exhibiting primary kraurosis and leukoplakic vulvitis with secondary kraurosis are small, but of a total of 14 patients in these two groups 8 were cured or markedly improved. Thus, by employing the combined local and parenteral hormone therapy more than 50 per cent of our patients

<sup>1</sup> We are indebted to Dr. L. Pirk of Roche-Organon, Inc., Nutley, N. J., for generous supplies of an ointment containing estrone (Menformon Dosules) and the estradiol benzoate ampuls (Dimenformon Benzoate).



suffering from these degenerative disorders were benefited.

A patient was classified as cured only if a follow-up study over a period of 12 months showed her to have remained symptom-free.

#### CASE HISTORIES

*Patient F.B.*, 63 years of age. Menarche at 12.5 years. Menstruation without cramps lasting 4 to 5 days, had occurred regularly every 4 weeks with a moderate amount of bleeding. There were 2 normal births and 3 induced abortions. The menopause occurred at the age of 49. Since that time there has been hypertension. The chief complaint was excruciating itching of the genitalia which prevented sleeping. *Pruritus vulvae which began at the age of 60 had gradually progressed to the perineum and then to the anal region.* Various local treatments including silver nitrate and a novocaine-menthol salve brought only temporary relief. Finally roentgen-ray treatment to the vulva was used resulting in some improvement for 3 months. However the pruritus recurred even more intensively.

The patient was moderately well nourished and gave the impression of being nervous and irritable. The blood pressure was 180/195 mm. Hg. Urinalysis was negative for albumin and sugar. The blood sugar was 120 mg. per cent. The heart showed enlargement of the left ventricle and accentuation of the second sound over the aortic area. There were varicose veins of the lower extremities. In the region of the genitals there were numerous scratch marks and shallow erosions on labia and in the region of the clitoris; there was partial lichenification of skin on labia majora and perineally. There was no discharge; no trichomonas vaginalis could be found. The pelvic examination showed nothing noteworthy. Rectoscopy revealed atrophic proctitis in the region of the sphincter. A diagnosis of essential pruritus vulvae was made.

An estrogenic ointment, containing 5000 I.U./gm. (estrone) was prescribed for use twice a day, and was to be rubbed into the vulval tissues. The itching increased after the second application of the estrogenic salve; however, on the fourth day the pruritus diminished, disappearing only from the anal region after one week of treatment. In the second week injections of estradiol benzoate, 10,000 R.U., were instituted. This dose was given twice a week and the salve was applied the days when there were no injections. At the end of the third week the pruritus disappeared completely. The patient slept well and expressed a sense of well being. From the fourth week, 10,000 R.U. of estradiol benzoate was injected once a week, local therapy being continued daily at the same dosage level as first prescribed except when parenteral medication was given. After completion of the 12-week period of treatment the patient remained free of complaints for one year, the period over which she was observed.

*Patient J.K.*, 69 years of age. Menarche at 14 years. Menstruation lasting 6 days had occurred every 4 weeks, unaccompanied by menstrual mclimic. There were 4 normal births and 2 abortions. Menopause was at the age of 49.

The chief complaints were genital itching, nervousness and insomnia. She had been suffering from the pruritus for 1.5 years and during this period 'local treatment,' the nature of which she did not specify, was given with only temporary relief. Roentgen-ray therapy was used without beneficial effect.

The patient was undernourished. The blood pressure was 165/90 mm. Hg; the urine negative for albumin and sugar; the blood sugar, 110 mg. per cent. A general physical examination showed nothing remarkable. Pelvic examination revealed an atrophic uterus, cervix flush with vaginal vaults. On both labia accentuated in the region of the clitoris, there were patches of whitish opaque and partly fissured lesions. There were atrophic changes and scratch marks in the surrounding areas. Vulval biopsy showed collagen degeneration of the subcutaneous tissue; the skin devoid of pigment and there was atrophy of the papillary body. There was hyperkeratosis and parakeratosis. A diagnosis of kraurosis vulvae was made.

Inunction with an estrogenic salve containing 5000 I.U./gm. (estrone) was prescribed for use twice a day. After 8 days of local treatment there was complete relief of pruritus during the day. At night, however, severe itching continued, rendering the patient sleepless. In the second week injection of 10,000 R.U. of estradiol benzoate was instituted twice a week. The topical medication was employed on those days when no injections were given. Combined local and parenteral treatment brought about a better blood supply to the atrophic regions of the genitalia. In the eighth week the parenteral dosage was decreased to 10,000 R.U. a week, inunction being continued twice a day. The atrophic foci had gradually become much smaller and in the eighth week of treatment the pruritus disappeared completely. The patient felt very well after treatment was discontinued after 12 weeks. She remained free of symptoms for one year, after which time she was not seen.

*Patient B.H.*, 61 years of age. Menarche was at 14 years. Menstruation accompanied by cramps and backaches, and lasting 2 to 3 days had occurred every 3 weeks. Nulligravida. Menopause was at the age of 45. Syphilis had been contracted in her twenties and had been treated.

The chief complaint was of severe itching of the genitalia, from which the patient had been suffering for the last year. Various kinds of treatment were given without success, including roentgen-ray therapy.

The patient was a moderately well nourished person with a blood pressure of 140/85 mm. Hg. Urinalysis was negative for albumin and sugar; the blood sugar, 95 mg. per cent. A general physical examination revealed nothing of significance. The patient gave the impression of being very nervous. The

re several leukoplakic foci and fissures in the region of the vulva, as well as shallow ulcerations at the anterior commissure. There were no local lesions in the vagina; the uterus was atrophic. A diagnosis of leukoplakia vulvae was made.

Therapy consisted of local application of a hormone ointment containing 5000 I.U. of estrone to be used twice a day. Healing of the fissures and ulcerations occurred in the second week and was accompanied by cessation of the pruritus. Ten days after institution of therapy parenteral treatment was started using

diphtheria. At the age of 4 a severe pruritus vulvae developed which was relieved to some extent by symptomatic treatment; however, as the mother told us, there were recurrences at certain intervals.

The patient gave the appearance of a healthy, normally developed child. Tuberculosis and syphilis were absent. A complete physical examination<sup>2</sup> revealed nothing remarkable. There were no skin lesions other than those at the vulva. Repeated urinalysis did not show any deviation from normal. No worms or their eggs could be detected in the stool. The hemo-

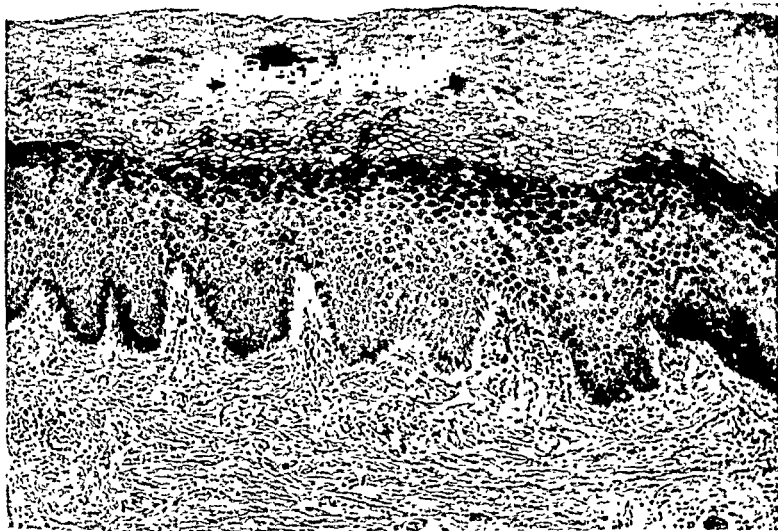


Fig. 1. Biopsy of vulval tissue of 6-year-old patient, G. H., revealing leukoplakic vulvitis.

000 R.U. of estradiol benzoate twice a week. The anal inunction was maintained on days between injections. The blood supply of the skin improved noticeably during the following weeks. The opaque whitish plaques became smaller and the fissures disappeared completely. Itching occurred only at night but it was less frequent and less intense. Beginning with the eighth week the parenteral dosage was decreased to one injection of 10,000 R.U. of estradiol benzoate a week. After completion of the 12-week course of therapy there was no pruritus, no ulcerations and no fissures, with only minute opaque foci. The symptoms did not recur during the follow-up study of 1 year.

The child who was observed and successfully treated is the youngest patient with leukoplakia and kraurosis vulvae on record so the complete case history is given.

Patient, G.H., 6 years of age had had measles and

globin was 78 per cent and the color index 0.88. A blood count showed 4,490,000 erythrocytes per cu. mm. and 8,400 leukocytes per cu. mm. The blood platelets were normal in number. There was a moderate anisocytosis and a slight anisochromia. The white blood picture did not show a shift to the left. However, there were 2 per cent of eosinophilic cells. The large monocytes were of normal structure; there was a lymphocytosis of 48.5 per cent.

Around the clitoris and the region of the labia minora there appeared opaque, whitish, circumscribed areas which were confluent, giving the clinical picture of leukoplakia vulvae. Biopsy revealed a marked hyperkeratosis and parakeratosis associated with pronounced edema of the subepithelial layers. The papillae were flattened and atrophic. In the subepithelial

<sup>2</sup> We are indebted to Dr. R. Wagner of Massachusetts, for pediatric examination of this

layer there was an extensive infiltration of lymphocytes and plasma cells; these were most marked within the papillary layer. The histologic picture of the excised specimen was typical of leukoplakia vulvae (fig. 1).<sup>3</sup>

Later there appeared small circumscribed atrophic areas above the clitoris and within the labia minora and tiny folds became apparent; in the subsequent course of the disease a kraurosis vulvae developed in addition to the leukoplakia. There was a fragmentation and decrease of the elastic tissue fibers and a marked atrophy of the papillae.

The child was subjected to the same type of therapy as used in the previous cases; however, the dosages of estrogenic hormone employed were much smaller than those administered to the adult patients. In the first week inunctions containing 2000 I.U. of estrone each, twice a day were applied to the vulva. In the second week 2000 R.U. of estradiol benzoate were injected intramuscularly every 3 or 4 days and on the days she did not receive injections ointment application to the vulva was continued each morning and evening using a total of 4000 I.U. for the day. After 3 weeks the injections were discontinued, only local treatment twice a day being administered using 2000 I.U. of estrone each time. Four weeks after institution of therapy there was marked improvement in the condition. The pruritus had subsided and the mucous membranes of the external genitalia were well supplied with blood. The whitish areas diminished in size but the kraurosis at this time did not show signs of improvement. The inunction was continued for a total of 12 weeks and a remarkable improvement of all the affected tissues was achieved. Considering the age of the patient and the excellent clinical response, it was thought inadvisable to take a post-medication biopsy specimen for histologic study.

#### DISCUSSION

The majority of cases of essential pruritus vulvae, kraurosis vulvae and leukoplakic vulvitis occur after the menopause. In view of the fact that a high percentage of cures in such cases is effected by estrogenic therapy, it is apparent that declining ovarian activity is an important etiologic factor. However, there are other causative factors in the pathogenesis of these disorders such as predisposition of the vulval tissues, familial factors and probably other factors unknown to us. That constitutional factors play a rôle is manifested by the fact that only a small fraction of menopausal women suffer from pruritus or kraurosis vul-

vae; furthermore, such disorders are found women of the reproductive age group, even girls shortly after puberty, and in our series, the case of the 6-year-old child. Among the familial factors in cases of essential pruritus vulvae were found disposition toward functional ovarian disturbances, myomata, obesity, metabolic disorders and diabetes, as well as functional disturbances of other glands.

It is significant that of the cases of kraurosis and leukoplakia which were refractory to hormone treatment, the majority belonged to the group of young women with apparently normal ovarian function. Failure of therapy in all likelihood indicates that in these instances elements other than decreased ovarian activity were etiologic factors in the disorders. The importance of vitamin-A deficiency has been stressed. Also it is noteworthy that over 13 per cent of our patients with kraurosis and leukoplakia, the etiology of which still remains obscure, had a previous syphilitic infection.

Of the 9 pruritus cases in patients with apparently normal ovarian function, 3 were cured and 2 were markedly improved by treatment. It may be assumed, although there is no conclusive evidence, that these 5 had an estrogenic deficiency as an underlying cause of the disease. However, the estrogen in these instances might have acted pharmacodynamically.

#### SUMMARY AND CONCLUSIONS

A series of 68 cases of essential pruritus vulvae, kraurosis vulvae and leukoplakic vulvitis with secondary kraurosis is presented. A treatment scheme, employed in all instances and consisting of local application of estrone ointment and parenteral administration of estradiol benzoate, is outlined.

Careful evaluation of results shows that in the group of 54 pruritus cases, 74 per cent were cured or markedly improved. There were 6 cases with primary kraurosis and 8 with leukoplakic vulvitis and secondary kraurosis. Of these 14 patients, 8 were either cured or markedly improved. Among the cured was the unique case of a 6-year-old girl with leukoplakia vulvae and subsequent kraurosis changes. The case history of this patient is given in detail. Also, 3 other case histories are presented.

<sup>3</sup> We wish to express our appreciation to Dr. Paul Klemperer, Clinical Professor of Pathology at Columbia University and Attending Pathologist at Mt. Sinai Hospital, who inspected this specimen and confirmed our diagnosis.

he importance of ovarian failure in the rogenesis of these disorders is stressed. ver, it is suggested that causative factors r than hypoövarianism may play an im- ant part. It is in these instances particu- r that estrogenic treatment might fall t of expectations.

nce no other method of therapy affords as e a percentage of cures in cases of this type oes the use of combined local and parent- administration of estrogenic hormone, s of essential pruritus vulvae, kraurosis vae and leukoplakic vulvitis should be n the benefit of this type of treatment.

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# Effect of Estradiol and Diethylstilbestrol upon the Atrophic Human Buccal Mucosa with a Preliminary Report on the Use of Estrogens in the Management of Senile Gingivitis

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IT HAD BEEN noted by one of us (A. R. A) that many climacteric patients complain of a dryness or burning sensation in the mouth. Following therapy with estradiol or diethylstilbestrol, these symptoms would disappear. An investigation of the literature disclosed that the reports on this subject were few. Nathanson and Weisberger (1) clearly described the associated gross lesions before and after treatment with estradiol, but they made no report of a microscopic study. In the castrated female monkey, Ziskin described stimulation and growth of the gingival mucosa following treatment with estrone and estradiol (2). In the human female, on the basis of a single biopsy specimen from each of 3 patients receiving estradiol, Ziskin concluded that estrogen stimulates growth and keratinization of the gingival mucosa (3).

These studies were made in view of the incomplete reports on mucosal response to estrogens in human beings. Estradiol and diethylstilbestrol were used in order to determine if there was any difference in their action. The substances used were estradiol dipropionate,<sup>2</sup>

diethylstilbestrol<sup>3</sup> and diethylstilbestrol monomethylether.<sup>4</sup> The latter two were administered orally. The estradiol dipropionate and monomethylether of diethylstilbestrol were injected either intramuscularly or locally under the buccal mucosa.

Twenty-five climacteric patients, observed for 3 to 18 months, form the basis of this report. In 17 patients, the menopause had been induced surgically. Gross oral manifestations, subjective symptoms and the histologic structure of the buccal mucosa before, during and after treatment were correlated. Biopsies were made under local anesthesia from the region of the buccal mucosa opposite the first and second molars. Vaginal biopsies were made, if there was an atrophic condition as determined either grossly or by vaginal smear. Since these studies will be reported in detail elsewhere (4) the results obtained will be briefly presented for their endocrine interest.

## *Correlation of Visual Oral Manifestations with Subjective Symptoms and Biopsies*

*Observations before treatment.* In general, the longer the interval of time since the menopause, whether surgical or spontaneous, the

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<sup>2</sup> The estradiol dipropionate (Di-Ovocylin) was supplied by Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, N. J.

<sup>3</sup> The diethylstilbestrol (Estrobene) was supplied by A. A. Ebby of Ayerst, McKenna and Harrison, Inc., Roseton Point, N. Y.

<sup>4</sup> The diethylstilbestrol monomethylether (Monomestrol) was supplied by Dr. W. Salmon and Dr. F. Schmeller of Wallace and Tiernan, Inc., Belleville, N. J.

more frequent were the varying degrees of atrophy and hyperkeratosis of the buccal mucosa. Within 6 months after the cessation of menses, the oral mucosa tended to be a normal rosy pink in color, moist and smooth. Biopsies revealed a normal histologic structure. In patients in whom the menopause had occurred 6 months to 2 or more years before, the mucosa usually was pale, grayish pink and anemic in appearance. At about this time, complaints were made of a dry or burning sensation in the mouth. Biopsies usually disclosed beginning atrophy of the prickle cell layer with an occasional early keratosis of the corneal layer.

In those cases in which the menopause had occurred more than 2 years before, milky, whitish or gray areas were noted more frequently, occurring either diffusely or in patches. At the same time the gingivae were observed to bleed easily, especially when the teeth were brushed or on slight pressure. Burning or dryness of the mouth was complained of more frequently. Biopsies of the buccal mucosa disclosed that atrophy of the prickle cell layer in these patients was more advanced while keratinization of the corneal layer was more marked. Macroscopically there were areas in which there was a milky white adherent film. Tissue from these regions showed a true leukoplakia on microscopic examination.

In both the early stages of simple atrophy and the later stages of keratosis and leukoplakia the histologic resemblance to similar lesions of the vulvovaginal tract was striking. No definite correlation, however, of the condition of the vulvo-vaginal mucosa and the buccal mucosa could be found.

*Observations after treatment.* With the exception of the leukoplakic areas in some patients, the mucosa became a normal bright pink in color following treatment. Several reported an increased salivation. The sensation of burning or dryness and the tendency for the gingivae to bleed disappeared early. Histologically, the following changes were observed. There was a marked increase in the vascularity of the sub-mucosal area, especially evident in the rete papillae. The basal layer which showed the most dramatic changes was greatly increased in thickness. The cells were larger. Occasional

mitoses were found. The corneal layer became thicker and showed more keratinization. On the other hand, the leukoplakic areas showed no increase in keratosis and in some instances there was a decrease.

It was found that injection of estradiol dipropionate locally into the buccal mucosa was the most effective and efficient method of administration. Concomitantly the hot flushes were also relieved. Both diethylstilbestrol and estradiol had the same effect upon the atrophic buccal and vaginal mucosa.

#### DISCUSSION

From the results obtained in this study, it is apparent that the natural steroid, estradiol, and the synthetic nonsteroid, diethylstilbestrol, are equally efficacious in restoring the atrophic buccal mucous membrane to a normal condition. The gross observations in these cases are in agreement with those of Nathanson and Weisberger except that they noted grossly a disappearance of the leukoplakic areas, while, as a rule, we did not. The microscopic observations confirm those of Ziskin in the monkey, indicating that the cellular reactions are similar in the mucosa of the human female and the monkey.

In its broader aspects, these studies supply additional evidence that the so-called 'sex' hormones are chemical substances capable of materially influencing many diversified phases of the body economy and that these effects are independent of the hormone action upon the secondary sexual characteristics.

*Clinical implications.* From a clinical point of view, the observation that the gingivae no longer bled easily after treatment with estradiol or diethylstilbestrol is significant. This fact has now been utilized by one of us (M. J. R.) in the management of senile or atrophic gingivitis. In this condition, the gingivae develop atrophic changes as described herein. In addition, they are characterized by a free bleeding which occurs under any pressure or tooth-brushing. In a selected number of these cases, in both men and women, estrogenic therapy was administered. Since the experimental evidence had shown that local therapy was the most effective, this has been used as

the route of administration. Two methods of local application were tried. In some patients, diethylstilbestrol ointment was massaged into the gum tissues with rubber applicators. In other cases, estradiol dipropionate was injected directly into the muco-buccal fold adjacent to the area to be treated. Of the two methods, the injection technique proved more effective. The inunction of diethylstilbestrol ointment, however, proved to be good adjuvant therapy after the initial result was obtained by injection. Bleeding from the gums ceased in all treated cases. These studies will be reported in detail elsewhere.

#### SUMMARY AND CONCLUSIONS

Gross oral manifestations, subjective symptoms and histologic structure of the buccal mucosa were correlated before, during and after treatment with diethylstilbestrol, diethylstilbestrol monomethylether and estradiol dipropionate in 25 climacteric patients.

Following the menopause a sequence of atrophic changes in the buccal mucosa may develop in the course of several months or years. Grossly, the normal bright pink color may become pale and anemic. Later, grayish white areas may appear diffusely, in patches or in streaks. Finally, areas containing a whitish adherent film may be observed. Associated with these atrophic changes, a sensation of dryness or burning may be noted by the patient. Histologically, the stratum germinativum atrophies; the corneal layer, with the lapse of time and under the influence of irrita-

tion which produces an abnormal growth stimulus, may develop leukoplakic areas.

The administration of estradiol or diethylstilbestrol provides a normal metabolic stimulus to the buccal mucous membrane. The latter develops a normal growth pattern. The prick cell layer hypertrophies, while the corneal layer becomes keratinized. The leukoplakic areas may tend to shrink. Grossly, the oral mucosa resumes its normal moist bright pink color.

Clinically, the sensation of burning and dryness disappears while the gingival bleeding is controlled. These findings have been utilized to good advantage in the management of senile atrophic gingivitis. The local injection of estradiol dipropionate beneath the muco-buccal fold proved to be the most efficacious method of administration.

The authors are indebted to Dr. H. C. Falk, Director, and Dr. P. M. Murray, of the Department of Gynecology and Dr. Louis H. Fairclough, Director of the Department of Oral Surgery, for permission to carry on this work.

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# Nutritional Deficiency in the Etiology of Menorrhagia, Metrorrhagia, Cystic Mastitis and Premenstrual Tension; Treatment with Vitamin B Complex<sup>1</sup>

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EVIDENCE relating the occurrence of certain forms of pathologic uterine bleeding, and of premenstrual tension, chronic cystic mastitis and other disturbances in an excess of estrogen has been accumulating over some years. This evidence was provided originally by the fundamental work of Frank and his collaborators (1-3). Other data have been summarized by several authors in recent authoritative symposia (4, 5). In addition to the investigations there described, Ehrlich (6) has observed in endometrium from patients bleeding abnormally, thrombotic phenomena similar to those illustrated by Zuckerman (7) in the endometrium of castrated monkeys treated with estrogen.

By utilizing an ingenious method devised by G. R. Biskind (8, 9), in recent studies on rats, it has been shown that the liver loses its ability to inactivate estrogen in vitamin-B-complex deficiency (10-12). Addition of Brewer's yeast to the diet was found to restore the inactivating mechanism (12). The amount of estrogen inactivated by the liver could be controlled at will, by withholding the vitamin complex or by restoring it to the diet. At the same time it was found that the inactivation of androgen was not significantly impaired in vitamin-B-complex deficiency (13), thus leading to a serious alteration of the estrogen-androgen equilibrium. The phenomena de-

scribed occurred in the absence of detectable gross or histologic lesions in the liver. Significant diminution in the ability of the liver to inactivate estrogen occurred in some animals with only a slight or moderate degree of vitamin B deprivation. In previous papers (11-13), we have pointed out some of the possible consequences of the rise in body estrogen and alteration of the estrogen-androgen equilibrium which occur in vitamin-B-complex deficiency.

On the basis of these investigations, it seemed worth while to determine whether there was a clinical correlation between nutritional deficiency and the occurrence of syndromes related to an excess of estrogen. Accordingly, a study was undertaken to determine whether patients with signs and symptoms of nutritional deficiency had menorrhagia, metrorrhagia, painful breasts, premenstrual tension or a combination of these. Conversely every patient presenting one or more of these conditions was investigated as to her nutritional status. As a definite correlation was found, treatment of these endocrine conditions with vitamin B complex was instituted.

## CASE REPORTS

*Case 1. R.G., age 46, had had menorrhagia for 5 years. During this time two periods had been normal. These had occurred following a curettage 8 months before she was referred to the Beth Israel Endocrine Clinic. Bleeding had by that time become so profuse that radiation therapy was advised by the family physician. For more than 4 years before the curettage bleeding had been irregular occurring, at first, every 5 or 6 weeks, with an occasional longer interval, and*

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<sup>1</sup> Aided by a grant from the Winthrop Chemical Company, Inc., New York.



later at intervals as short as two weeks. Following the curettage the periods had been more regular, occurring every 25 to 30 days, but except for the two normal periods already mentioned, bleeding lasted 9 days. There was no history of tenderness of the breasts.

The height was 61 inches, weight 151 pounds. Gynecologic examination revealed no detectable abnormality in uterus or adnexae. There was a definite but not severe atrophic glossitis when she was first seen; the diet had been deficient for many years.

The patient was treated chiefly with a fortified preparation of rice bran extract<sup>2</sup> and, for part of the time, with a preparation derived from yeast.<sup>3</sup> The first subsequent period, after 3 weeks of therapy, appeared a week before it was expected; the flow was scant and lasted 3 days. By this time the tongue had completely healed. The next two periods occurred at the expected times; one lasted 6 days, the next, 3 days. Bleeding was much less profuse than it had been and the patient remarked that she felt much better during the periods than formerly.

*Case 2. M.G.*, age 42, had a severe atrophic glossitis, cheilosis<sup>4</sup> and ulcerations inside the lower lip. She had had menorrhagia for about 4 years; the menstrual periods occurred every 28 to 30 days and lasted from 4 to 10 days. Associated with the menstrual disorder and the oral signs of nutritional deficiency, there had been over a period of years a variety of physical and mental symptoms. She was depressed, apprehensive, exceedingly irritable and was concerned because she was getting increasingly short-tempered with her children. She had aches and pains in arms and shoulders and suffered from many headaches. These symptoms all became worse just before and during each period. They were so severe that she had had repeated psychotherapy, without apparent benefit. The diet had been deficient over a long period of time; whole grains and fresh fruits and vegetables especially were lacking.

<sup>2</sup> Fortified rice bran extract (Elixir Ribranex) supplied through the courtesy of the Research Laboratories of the S. M. A. Corporation, Chagrin Falls, Ohio. The usual dosage was 2 teaspoonfuls 3 or 4 times a day.

<sup>3</sup> This preparation (Blexin tablets) was supplied by the International Vitamin Corporation, New York through the courtesy of Mr. Milford H. Wise. The dosage employed was 6 to 8 tablets, three times a day.

<sup>4</sup> Cheilosis is a designation proposed by Sebrell and Butler in 1938 to describe lesions of the lips characteristic of riboflavin deficiency in human beings. The condition is described by Sebrell [Human Riboflavin Deficiency (Ariboflavinosis), in *The Biological Action of the Vitamins*, edited by E. A. Evans, Jr., University of Chicago Press, 1942, pp. 75-76] as follows: 'The changes . . . consisted of lesions on the lips, which began with pallor of the mucosa in the angles of the mouth. This pallor was soon followed by maceration; and within a few days superficial linear fissures, usually bilateral, appeared exactly in the angle of the mouth. These fissures showed very little inflammatory reaction, remained moist, and became covered with a superficial yellowish crust, which could be scraped off without bleeding. In some instances these linear fissures showed a tendency to extend onto the skin of the face but did not extend into the mouth. At the time the fissures were developing, the lips became abnormally red, shiny, and superficially denuded along the line of closure.' Cheilosis is considered synonymous with 'perlèche.'

Calorically, however, the diet was more than adequate, as she weighed 161 lb. and was but 64 inches in height. She had had a thyroidectomy 11 years before; the basal metabolic rate currently varied between minus 21 and minus 12. The thyroid was diffusely enlarged and prominent. Repeated attempts to administer thyroid had resulted only in increasing the patient's nervousness and irritability and it had to be discontinued. Gynecologic examination revealed no abnormalities in the uterus or adnexae.

For 5 months, *M.G.* received vitamin B complex orally, mainly a preparation derived from yeast 3 times a day with meals. After 5 weeks this was supplemented with thiamin 9 mg., riboflavin 6 mg. and nicotinamide 75 mg. per day in divided doses.

After two weeks of therapy, a period occurred which lasted 4 days; spotting occurred for two days; the flow was fairly profuse for the next two days. When the patient was seen at the end of this period the glossitis was much improved, the cheilosis unaffected. The next period occurred 30 days later, lasted 3 days and the flow was normal in amount. By this time the tongue had almost completely healed and the ulcers in the mouth had disappeared, but the cheilosis still showed no improvement. The subsequent 3 periods, which occurred at about 30-day intervals, lasted 2, 5 and 3 days, respectively, and were much less profuse than formerly.

After 4 months of therapy the glossitis, stomatitis and menorrhagia had improved markedly, but the cheilosis was still unaffected and the mental symptoms were only moderately improved. An intertriginous eruption on the thighs that had resisted dermatologic therapy cleared up completely. The patient was then given thiamin hydrochloride, 50 mg. intramuscularly, 3 times a week. After the second injection there was a striking improvement of the mental state; for the first time the patient was smiling and cheerful when she presented herself for treatment and except for occasional setbacks apparently due to persistent psychogenic factors, has continued so to the time of writing. Although riboflavin was administered only by mouth, when thiamin was administered parenterally, the cheilosis began to improve for the first time. The possible significance of this observation will be discussed later.

*Case 3. R.B.*, age 30, complained of menorrhagia alternating with intervals of amenorrhea for 6 years. When the patient was first seen, the last previous period had begun 25 days before, had lasted 9 days and the flow was moderately profuse. The previous period had occurred 3 months before that and had also lasted 9 days. Only a few weeks prior to this she had been admitted to the hospital for a curettage because of severe metrorrhagia. The endometrium had been hyperplastic and edematous and had showed no secretory change. An endometrial biopsy in 1938 had shown a similar histologic picture. In 1934 this patient had had a left oophorectomy because of a cystic ovary and a cholecystectomy. She had been under treatment for vaginal trichomoniasis for several months.

This patient was overweight (159 lb., height 61 in.) The basal metabolic rate was plus 5. The thyroid was slightly and diffusely enlarged. The tongue had a striking patch of atrophic glossitis about 1.5 cm. in diameter on the right posterior portion. She had been unaware of this lesion as the tongue had been tender or irritated. The diet had consisted chiefly of carbohydrates, no whole grains and few fruits and vegetables.

She was treated with rice bran extract<sup>2</sup> over a period of 3 months. Within 8 days the tongue had healed completely and the site of the previous glossitis was not detectable. The first subsequent menstrual period occurred after 7 weeks of therapy (10 weeks after the previous period), this lasted 6 days and the flow was normal in amount. The next period was 20 days later, lasted 5 days, and also was normal in amount.

*Case 4 M W*, age 15, complained of vaginal bleeding for the preceding 4 months. There was a continuous intermenstrual spotting which ceased for two days before each period. The menarche had occurred at age 13 and subsequent periods were scant and irregular, occurring every 2 to 6 weeks and lasting 5 days. The only definite sign of nutritional deficiency was edema of the tongue, which showed fixed, deep indentations from contact with the teeth. The diet had long been inadequate, apparently because of rebellion against an oversolicitous mother. The thyroid was slightly and diffusely enlarged. The hemoglobin was 80 per cent. She complained of frequent attacks of abdominal discomfort and pains in the lumbar region and legs. The attacks of abdominal pain had led to an appendectomy 3 years previously, without relief of the symptom. Rectal examination showed the uterus to be definitely enlarged. There were no other abnormalities.

This patient was given a preparation derived from yeast,<sup>3</sup> for a period of 2.5 months. There was no intermenstrual spotting after the first subsequent period, which occurred after a 29 day interval and lasted 4 days with normal amount of flow. The succeeding period occurred 34 days later, lasted 5 days and was normal in amount. The dosage of B complex was reduced about one half, after 11 days spotting began again. The amount of B complex was increased to the previous level and the spotting stopped after 3 days and has not again recurred. During the 2.5 months of therapy, there was a striking improvement in general physical appearance and there have been no further attacks of pain in abdomen, back or legs. The edema of the tongue likewise disappeared.

*Case 5 F H*, age 39, chiefly complained of crusted lesions about the nares and upper lip of two years' duration, dating from the birth of her baby. She had a deeply fissured tongue and puffy, bleeding gums. She had felt continuously 'exhausted' since childbirth and has had a progressively increasing feeling of 'incompetence,' and an inability to cope with life in general. Her memory for recent events had become so poor as to prove embarrassing and alarming, occurrences of

the morning were already vague and distant by evening. She complained of numbness and pain in arms and hands, especially at night. The last menstrual period had been so profuse that she had been afraid she 'had a hemorrhage.' She could not remember its exact duration. She recalled that for several years she had usually passed large clots during menstruation but had not thought this abnormal. The breasts were usually tender for several days before each period, there was no palpable mastitis.

This patient was given rice bran extract,<sup>2</sup> 4 times a day. The first subsequent period occurring after 3 days of therapy, was quite profuse and lasted 3 days. Two and a half weeks later, there was a marked change in the appearance of the patient, she felt stronger and not so tired, her memory had improved moderately. The lesions on the upper lip and nostrils had almost completely healed and were nearly invisible, the glossitis had also improved. This case is included to show the correlation between signs of nutritional deficiency and menorrhagia.

*Case 6 S R*, age 35, had had persistently painful breasts since a pregnancy 5 years previously. Associated with this was severe premenstrual tension for the last week or 10 days of each intermenstruum. She had had psoriasis for 12 years and rheumatic arthritis for 8 years (so called arthropathic psoriasis). For several years, in addition to the painful breasts (the pain and tenderness were more marked on the left side), there had been repeated attacks of redness and swelling of the left breast associated with high fever of several days' duration. On a few occasions this had proceeded to abscess formation and required surgical drainage. Usually these attacks occurred one or two days before the onset of menstruation, a few had occurred on the last day of the period. For about 6 months she had received estrogen therapy and there had been a diminution in the severity and frequency of the attacks of mastitis, subsequently, however, while she was still receiving estrogen therapy, two severe attacks occurred during the intermenstruum. She was then advised to have a left mastectomy as the only adequate therapeutic solution. At this time she was referred to the Beth Israel Endocrine Clinic.

The menstrual history of this patient was not remarkable, the periods occurring every 26 or 27 days and lasting 3 or 4 days, the flow was normal in amount. Gynecologic examination had revealed no abnormalities in uterus or adnexae. She was 64 inches tall, and weighed 170 lb. She had two children, 11.5 and 5 years of age. There had been no other pregnancies. The basal metabolic rate was minus 4. Both breasts were tender and nodular, the left more so than the right. There was a large patch of psoriasis under each breast and similar lesions on the thighs and scalp. There was pain on movement of fingers, wrists, ankles and toes but this was not sufficient to be disabling and there was no swelling or limitation of movement in these joints at the time of examination. At this time also, there were no lesions in the mouth which suggested nutritional deficiency, although there was a history of

cheilosis at the angles of the lips before each period (a severe attack of cheilosis appeared subsequently). The diet had been very limited for several years because of restrictions imposed for the treatment of the psoriasis. She had been taking 50,000 units of vitamin A daily.

For more than 4 months S.R. received a preparation derived from yeast,<sup>3</sup> taking it 3 times a day. The tenderness and nodular quality of the breasts disappeared and the patient remained free of mammary pain and tenderness for 3.5 months. Simultaneously, the premenstrual tension subsided almost completely. The symptoms recurred and the breasts again became nodular about two weeks after the vitamin therapy was stopped (one week after the previous period). She was impressed with the necessity of continuing the vitamin therapy, which she did after a total lapse of 4 weeks. One week after the subsequent period there was another attack of redness and swelling of the left breast with a fever of 103° F. This subsided completely in two days. Following this a severe cheilosis developed involving the whole of both lips and patches of the skin about them. The dosage of vitamin B complex was then increased, another product<sup>5</sup> being substituted. At the same time the patient was advised to include in her diet liver, pot cheese and liberal quantities of whole grains, fruits and vegetables. Two months later there was only slight tenderness of the breasts, which were now much less nodular. There had been no premenstrual tension during this interval and no acute mastitis. Except for the lesions on the scalp, the psoriasis had improved markedly; the patches under the breasts were now much smaller. There had been no attack of arthritis since the therapy was begun, the first time since the disease had started 12 years before that she had gone through even part of the winter free of joint pain. Aside from this improvement, the patient was enthusiastic over the state of her health.

*Case 7.* P.W., age 35, had a nutritional deficiency secondary to chronic enteritis of 9 years' duration. There was a history of menorrhagia and cystic mastitis for the greater part of this time. The breasts had been nodular and continuously painful for several months at a time. The mastitis had been treated successfully with estrogen over a period of 6 months. The menorrhagia later gradually regressed (she had subsequently received vitamin B complex orally as treatment of the enteritis). Several years afterward, although oral B complex had been continued in the meantime, the breasts began to be painful for the latter 2 or 3 weeks of each intermenstruum. This was associated with premenstrual tension. Following treatment parenterally with a B-complex preparation derived from liver, the mammary tenderness subsided and the nervous tension diminished about 12 hours after each injection, recurring in 24 to 36 hours. Therapy with this preparation was interrupted for several months be-

cause of the development of sensitivity to the extract. During this time the mastitis and premenstrual tension became progressively worse each month. Then for 5 months, a mixture of synthetic B vitamins<sup>6</sup> was injected intramuscularly every second day (in each dose, thiamin 10 mg., riboflavin 5 mg., pyridoxine 5 mg., calcium pantothenate 5 mg., niacin amide 50 mg.). The tenderness and nodular character of the breasts rapidly regressed and there has been no mammary pain or tenderness for more than 4 months. During the first month of this therapy there was moderate premenstrual tension, during the succeeding 4 months virtually none. Coincident with improvement in the mastitis and premenstrual tension, acne which, for several years past, had appeared during the last one or two weeks of each intermenstruum, cleared up and has not recurred.

The necessity for adequate parenteral therapy where there is interference with enteric absorption, or failure otherwise to respond to oral administration, is emphasized in this case.

In addition to the cases presented there were 22 patients with atrophic glossitis, cheilosis or stomatitis, or a combination of these, who also had a history of menorrhagia, metrorrhagia or both. Six had painful breasts, 3 had severe premenstrual tension in addition. In two other cases with signs of nutritional deficiency, 'painful breasts' was the chief complaint; the menstrual flow was normal in amount in one, scant in the other. Among the 22 patients, 6 were in the menopause at the time they were first seen and all 6 had had premenopausal menorrhagia.

Of those with marked symptoms related to excess estrogen, 6 cases in addition to those presented in detail, were treated with rice bran extract.<sup>2</sup> All had menorrhagia; 3 had premenstrual tension also. All responded favorably to the vitamin B complex.

#### DISCUSSION

It has long been known that menorrhagia and metrorrhagia may occur early in the course of cirrhosis of the liver (14, 15). Excessive uterine bleeding has been reported also in intoxication with a number of liver poisons.

<sup>6</sup> Synthetic B vitamins (Betaplex Niphanoid) supplied by the Winthrop Chemical Co. I am indebted to Dr. J. B. Rice and Mr. W. E. H. Caldwell of the Department of Medical Research of the Winthrop Chemical Company, Inc., for an experimental supply of this preparation and of the Betaplexin referred to in footnote 5.

<sup>7</sup> In rats a mixture of the first four of these substances has been found capable of restoring the estrogen-inactivating function of the liver impaired by deprivation of the B complex—unpublished observations.

<sup>5</sup> Vitamin B complex (Betaplexin Capsules) supplied by Winthrop Chemical Co., New York City. The dosage employed in case 6 was 3 capsules 3 times a day.



have been able to produce such exacerbations by the administration of estrogen. Among the cases I have studied, in three cyclically recurring signs of B deficiency have been observed. One patient had a severe premenstrual stomatitis associated with cystic mastitis and premenstrual tension since the birth of her child 5 years previously. The stomatitis healed promptly with large doses of vitamin B complex orally<sup>2</sup> and parenterally.<sup>6</sup> Another patient, (case 6) had a history of cheilosis during the last week of each intermenstruum. A third patient (case 7) had premenstrual acne which disappeared under combined oral and parenteral therapy with B complex. The recent report of Jolliffe and his collaborators (41) on the response of acne to therapy with pyridoxine is of significance in this connection.

A study by Heilig and Kantiengar (42) on variations in liver function during the menstrual cycle may have a bearing on the reciprocal relation of estrogen and the vitamin B complex. These investigators found that in women in whom there is a relatively low liver function as measured by the Quick test on the 13th or 14th day of the menstrual cycle, there is a significant and further diminution in liver function on the first day of menstruation, *i.e.*, after the two-week period during which the peak or peaks of estrogen occur. In women who had excellent liver function in the mid-interval there was little change on the first day of bleeding. The percentage of decrease in liver function was greatest in those cases in which liver function at the mid-interval was lowest. In view of the known relation of the B complex to liver function, it seems not improbable that the first group mentioned had nutritional deficiency.

Four of the cases reported in this paper had had chronic vaginitis of long-standing; in 3 of these trichomoniasis was present. Vaginitis is a not infrequent occurrence in pellagra (31) and in less severe deficiency states (43). Shute (44, 45) has pointed out that in some patients with vaginitis and vulvitis, there is an excess of estrogen in the blood; at least one of the patients among those he has reported had a definite vitamin B deficiency with severe peripheral neuritis and mental depression. The exacerbations which occur in vaginitis, espe-

cially in trichomonas vaginitis, during the menstrual periods, may be related to depression of an already depleted vitamin B reserve by the high body estrogen preceding the onset of menstruation.

Two important features appear in this study. One was that several of the patients first developed syndromes related to an excess of estrogen immediately following a pregnancy during which time nutritional demands are increased but rarely met (46). Three of the women, significantly, had a subsequent subinvolution of the uterus. The other feature was the relation of these syndromes to obesity; most of the patients were overweight. One patient in particular, age 28, 61 in. tall, weighed 206 lb. Owing to psychogenic factors during times of family stress she would eat voraciously and gain as much as 50 lb. in a few months. Each time she gained weight, and there were three such episodes, severe menorrhagia and metrorrhagia developed. When she dieted and lost weight the excessive bleeding stopped. During the last bout of over-eating the bleeding was so severe that she was treated with radium.

It is now well known that the modern 'normal' American diet is generally a deficient diet (47, 48), especially with regard to the vitamins. Since the need for thiamin, for instance, is related directly to the caloric intake, it is easy to see that, in a diet in which there is less thiamin per 1000 calories than the minimum need, the greater the caloric intake the greater the thiamin deficit. In the cases reported in detail in this paper, the vitamin B complex was administered without any measures directed to reduction in weight. In other cases now being studied, both therapeutic measures are being employed concurrently.

The need for the B vitamins is also related to the metabolic rate (49). It is significant that in case 2, in which a severe nutritional deficiency was present, repeated attempts to administer thyroid because of a low basal metabolic rate led only to exacerbation of the symptoms of nervousness, irritability, insomnia and headaches. The increased metabolic rate thus induced enhanced an already severe nutritional deficiency. In this case also, a further point is of interest. Oral administration

of riboflavin (with the rest of the B complex) over a period of several months failed to affect the cheilosis in any degree although an accompanying glossitis and stomatitis healed rapidly. When thiamin alone was given parenterally, while the remainder of the complex was given only by mouth, there was prompt and definite improvement in the cheilosis. This may be related to the observation by Sure and Ford (50) that in thiamin deficiency there is a disturbance in riboflavin metabolism owing to failure of absorption.

It may appear paradoxical that the mastitis was successfully treated in case 7 (and with somewhat less success in case 6) at one time by giving estrogen and at another time by therapy that might be expected to diminish the body estrogen. However, Gardner (51) has shown that while moderate doses of estrogen in animals stimulate mammary growth, larger doses depress it.

The B complex preparations used orally in this study were usually given in doses providing daily from 3 to 9 mg. of thiamin, from 4.5 to 9 mg. of riboflavin, up to 60 mg. of niacin and niacin amide. The necessity for adequate dosage of vitamin B complex preparations in the treatment of deficiency states cannot be too strongly emphasized. And, as failure of absorption occurs frequently in B complex deprivation, adequate parenteral therapy is often necessary.

It is of interest in connection with the observations reported in this paper that empirically, liver extracts have been used in the treatment of menorrhagia and metrorrhagia (52, 53). It seems likely, from unpublished observations on animals, that the liver fractions owe their effectiveness in pathologic uterine bleeding to their activity in restoring the estrogen-inactivating function of the liver, impaired by nutritional deficiency.

#### SUMMARY

Evidence is presented that menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension and possibly other syndromes related to an excess of estrogen, are caused by failure of the liver to inactivate estrogen because of deficiency of the vitamin B complex. Administration of the B complex in adequate dosage

orally, parenterally, or by both routes, led to prompt improvement in these conditions.

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# Effect of Androgens upon Libido in Women

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**D**URING the course of the therapeutic administration of androgens for various endocrinopathic gynecologic disorders during the past five years, the observation was made that libido was apparently increased in a number of the women being treated (1). Our attention was first drawn to this phenomenon in 1937 by an ovariectomized woman, suffering from the menopause syndrome, who was being treated experimentally with testosterone propionate. During the course of treatment the patient volunteered the information that she had experienced resurgence of sexual desire after a period of quiescence of some ten years. Since then we have been conducting a series of studies to determine the effect of various sterol sex hormones upon the psychosexual reactions of women.

## METHODS AND MATERIALS

The present report is based on our observations of a series of 101 women comprising the following groups. *Group A.* Twenty-nine cases of primary frigidity which were being treated for some apparently unrelated gynecologic disorder: dysmenorrhea, 6 cases; menometrorrhagia, 16 cases; polymenorrhea, 3 cases; premenstrual tension, 4 cases. *Group B.* Thirty cases of secondary frigidity occurring a) at the menopause, 13 cases; b) after bilateral ovariectomy, 7 cases; c) after roentgen-ray castration, 7 cases; and d) in association with menorrhea, 3 cases. *Group C.* Forty-two were patients with apparently normal libido who were being treated with androgens for one of the following complaints: dysmenorrhea, 12 cases; menorrhagia, 27 cases; and premenstrual tension, 3 cases.

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*Types of androgen therapy and dosage used.* Fifty-six of the patients were treated with testosterone propionate in sesame oil intramuscularly in doses of 10 or 25 mg. two or three times weekly, the total weekly doses varying from 20 to 75 mg., for periods varying from 6 to 8 weeks; 22 with methyl testosterone in daily doses of 10 to 30 mg. orally for periods varying from 3 to 6 months; 23 received subcutaneous implants of 2 to 8 pellets of testosterone, each weighing 75 mg. Periods of observation following therapy varied from 8 to 38 months.

## RESULTS

### *Group A. Primary Frigidity with Somatic Gynecologic Disorders*

Of the 29 cases in this group 21 were treated with testosterone propionate intramuscularly and 8 had pellet implants of testosterone. Of the 21 cases treated with testosterone propionate, 4 reported excessive sexual stimulation. These patients were conscious of a sensation of formication in the vulva which was most marked in the region of the clitoris. The clitoris and prepuce were hypersensitive and in two cases, slightly hypertrophied. Ten of the cases reported complete sexual gratification, 4 reported considerable improvement but were unable to achieve an orgasm and 3 reported no improvement.

Of the 8 cases with testosterone pellet implants 2 reported excessive stimulation (600 and 525 mg., respectively); 4, normal sexual reactions (225 to 450 mg.); and 2, no response (150 and 300 mg.).

Of the 5 failures in the group of 29 cases, 2 could be attributed to marital incompatibilities. In the remaining 3 there was a heightened clitoral sensitivity without, however, consonant emotional response. These 3 individuals appeared to be normal, well-in-



formed, well-adjusted women who professed to be, otherwise, happily married.

*Group B. Secondary (Endocrinopathic) Frigidity*

In order to evaluate the effect of androgens in the presence of an estrogen deficiency the 30 patients with secondary or endocrinopathic frigidity were divided into three groups and treated as follows: *a*) one group of 10 received androgens; *b*) another group of 11, estrogens, and *c*) the remaining 9 cases, androgens and estrogens simultaneously.

*Effect of androgens in estrogen-deficient cases.* After periods of treatment varying from 4 to 8 weeks, the total doses varying from 240 to 600 mg. of testosterone propionate, 9 of the 11 patients in this group reported increased libido and increased clitoridal sensitivity, but did not experience coital gratification. One patient reported excessive stimulation and one none at all. The 9 stimulated patients stated that coitus could not be satisfactorily consummated because of dryness and tenderness of the vagina. Following the course of androgens, estrogens were substituted for the testosterone without the patient's knowledge (2.5 mg. of estradiol dipropionate three times weekly). After treatment with estrogens for 10 to 14 days, the patients reported disappearance of the vaginal dryness and tenderness and they were able to perform coitus satisfactorily. This improvement in the subjective vaginal reaction paralleled the appearance of a characteristic estrogenic effect in the vaginal smears.

*Effect of estrogens in estrogen-deficient cases.* Twelve patients were treated with estrogens (2.5 mg. of estradiol dipropionate three times weekly) until the vaginal smears showed a full estrogenic effect, and the vasomotor symptoms were relieved. Libido was not, however, appreciably affected. Eight patients of this group who, prior to the estrogen therapy, had experienced dyspareunia caused by 'senile' vaginitis and who had in consequence developed a distaste for coitus, were relieved of the coital discomfort after treatment with estrogens, but none of these reported a resurgence of libido. At this point, without their knowledge, androgens were substituted for the estrogens (25 mg. of testosterone propionate

2 or 3 times weekly). After approximately 3 weeks, 4 patients reported restoration of normal sexual reaction; 2, excessive stimulation; 1, slight, and 1, no improvement.

*Effect of combined estrogen and androgen therapy in estrogen-deficient cases.* The 9 patients in this group were given estrogens and androgens simultaneously, 1 to 5 mg. of estradiol dipropionate in combination with 10 or 25 mg. of testosterone propionate two or three times weekly. In 7 instances, the patients reported a marked improvement after 3 or 4 weeks of treatment. The optimal therapeutic effect was obtained in these cases when the vaginal smear revealed a full estrogenic effect even though the androgens were being given. If sufficient androgen, but insufficient estrogen was given, the patient experienced the stimulating effect of the former but coitus was unsatisfactory and a vaginal orgasm was not achieved, because of the dryness and irritability of the vagina; when, however, an adequate amount of estrogen but an insufficient amount of androgen was given, the vaginal dryness and irritability were relieved but libido was not stimulated.

*Group C. Cases with Somatic Gynecological Disorders and Normal Libido*

Of the 42 patients in this group 10 were treated with testosterone propionate, 25 mg. twice weekly or 10 mg. three times weekly, intramuscularly; 12 with methyl testosterone orally, 20 to 50 mg. daily. Fifteen received implants of testosterone pellets, 75 mg. each, total doses varying from 300 to 600 mg.

*Results with testosterone propionate.* Of the group treated with testosterone propionate, all but one experienced increase of libido after receiving approximately 200 to 300 mg. With this dose a mild stimulation occurred which persisted for several weeks. Continued administration of the testosterone propionate resulted in a progressive increase of libido, in 4 instances to a distressing degree.

*Results with methyl testosterone.* Methyl testosterone produced moderate stimulation in doses of 20 and 30 mg. a day after treatment for 2 to 3 weeks. In 6 instances doses of 40 and 50 mg. a day caused excessive stimulation

er two weeks of treatment and it persisted approximately two weeks after discontinuation of the hormone.

**Results with pellet implantation.** Of the 15 cases in this group receiving pellet implants of testosterone, 3 reported no change (150 mg., 2 cases; 300 mg., 1 case); 5 were moderately stimulated for 4 to 5 weeks (150 mg., 1 case; 5 mg., 1 case; 300 mg., 3 cases). Seven were excessively stimulated for 6 to 8 weeks (450 mg., 3 cases; 600 mg., 4 cases). Subjective evidence of stimulation was reported in 10 of the responsive cases approximately 12 days after the implantation; in 2 cases implanted with 150 mg. increased libido was not noted until approximately 18 days after the implantation.

#### DISCUSSION

It appears from this study that androgens have a triple action upon the psychosomatic sexual mechanism, causing, *a*) a heightened receptibility to psychic stimulation; *b*) increased sensitivity of the external genitalia, particularly of the clitoris and *c*) a greater intensity of sexual gratification.

It appears, furthermore, that in the presence of an estrogen deficiency, androgens in the doses used may stimulate the psychic and the sensory components but that culmination in a vaginal orgasm may not be accomplished without the complementary stimulative effects of androgens upon the vagina. The estrogens cause increase in the vascularity of the vagina and increase the physiologic lubricant resulting from desquamation of the cornified epithelial cells and the cervical secretion which is essential for normal coital sensibility.

It is noteworthy that in 6 of the 13 cases which failed to respond to the androgens, there appeared to be some psychic disturbance to which the frigidity could be attributed. It would seem from these studies that types of frigidity that are predominantly psychogenic in origin are not responsive to androgen therapy. However, the stimulating effects of the androgens are so striking, that even psychogenic types might be benefited, providing one can be reasonably certain that the stimulation

would not *per se* cause undesirable psychic repercussions.

The question arises as to whether this stimulating action of the androgens upon the psychic and somatic components of the sexual mechanism should be considered as a pharmacologic phenomenon or whether one may infer from these observations that in the normal female some endogenous androgens may have a similar effect, acting as a physiologic stimulant or activator of the psychic and somatic components of the sexual mechanism. For several years we have fostered the theory that androgens play an important rôle in the steroid sex hormone physiology of the human female, modifying and balancing the action of the gynecogenic hormones (1, 2, 3). We have based the rationale for the use of androgens in the treatment of certain types of menometrorrhagia (4, 5), dysmenorrhea (6), and premenstrual tension (1, 7) upon this theory. It appears from the studies herein reported that the endogenous androgens in the mature human female may have still another function, namely, to sensitize both the psychic and somatic components of the sexual mechanism so that the individual is emotionally receptive to excitation and somatically sensitive to sexual stimulation.

#### SUMMARY AND CONCLUSIONS

The effect of androgens upon libido was studied in a group of 101 women who were being treated for some endocrine disorder. The androgens were administered in the form of *a*) testosterone propionate in solution in sesame oil, intramuscularly; *b*) pellets of testosterone, implanted subcutaneously; and *c*) methyl testosterone, orally. All but 13 of the 101 treated women reported some increase in libido; 20 noted excessive stimulation which subsided within 2 to 4 weeks after discontinuation of the androgen therapy. From these studies it appears that androgens have a three-fold action, causing *a*) an increased susceptibility to psycho-sexual stimulation; *b*) an increased sensitivity of the external genitalia and *c*) a greater intensity of sexual gratification.

It is suggested on the basis of these observations that endogenous androgens in the normal

mature woman may act as the physiologic sensitizer of both the psychic and somatic components of the sexual mechanism.

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# Personality Changes in Endocrine Disorders

## With a Note on 'Symptomatic Hypoglycemia'

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PERSONALITY may be defined as a resultant of internal forces within an individual which affect his relationship to his environment. It may be regarded as a subjective concept and be subdivided into such components as impulse, temperament, character and intelligence<sup>1</sup> (1). It is a form of 'potential energy,' a summation of attributes which can be brought to bear in the individual's dealings with the world. When it is expressed and becomes kinetic or active, one may designate it as behavior, an objective concept. To evaluate properly the endocrine glands as active causes or even as precursors of personality change, it is necessary to understand the mechanisms involved in any disease-personality relationship. These are the structural, the functional and the psychogenic.

### *Structural Mechanism*

The most fundamental aspect of structure is the constitutional make-up of the individual. His hereditary factors express themselves in certain body types (pyknic or leptosomic) with a resultant predisposition toward one or another form of personality or mental disease (manic-depressive or schizophrenic). Various other classifications of constitutional types have been evolved, but it is just as wrong to explain all disease entities from the constitutional viewpoint as to ignore this fundamental subject. An intercurrent disease, of whatever nature, with its personality alteration must

consequently be considered in the light of the inherent constitution which is the oldest and most primitive determinant of the personality pattern throughout life. Disease will not affect the underlying constitution but there is evidence that certain types of constitution may predispose to both physical and psychic disorders. Another type of organic or structural factor is found in the congenital anomalies. These somatic defects may originate in the germ plasm or arise during intrauterine existence. Anomalies in brain development fit into this category. They may cause profound personality abnormalities which are practically irremediable or may be so slight as almost to escape notice. Diseases such as mongolism, Laurence-Moon-Biedl syndrome and Turner's syndrome are examples of this type. A third type of organic mechanism which alters the personality pattern is represented by the pathologic changes incident to cerebral hemorrhage, infections and tumors. Endocrine manifestations are often observed concomitantly with these organic factors, since the pathologic process in the brain may eventually involve the pituitary and/or the hypothalamic centers. A whole chain of abnormal endocrine phenomena may thus be set in motion. Personality changes frequently observed early in patients with gigantism or acromegaly are examples of this type.

### *Functional Mechanism*

The second type of mechanism producing personality alterations is purely functional. It is also called symptomatic. Being due to altered biochemical or autonomic-nervous activity, it is most often reversible. For this reason, its

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<sup>1</sup> The concepts of personality advanced by Kahn, based as they are on the study of himself, are themselves idealized and subjective. The classification as inclusive and exclusive is a common-sense approach to the study of personality.

early recognition is important for the welfare of the patient. The toxic psychoses from acute infections, drugs and alcoholism are here represented. Alterations in the female psyche with the menarche, menstruation, pregnancy and the menopause are similar examples. Endocrine disorders in general affect personality most frequently through this functional mechanism. They do so primarily through an increase or decrease of the impulse and emotional tension. The effect is non-specific in the sense that it swings mood or tempo in either direction. The hyperkineses and increased drive with or without irritability are seen in hyperthyroid patients and their converse in hypothyroidism. Similarly, the gonads appear primarily to influence impulse and emotional tension. Superimposed psychogenic reactions due to difficulties in coping with the environment and even major psychoses (manic depressive or schizophrenic) may be precipitated as secondary effects.

A frequent functional mechanism affecting personality reactions and one found with or without endocrine disease, is hypoglycemia. In this condition there occurs a depression of the blood-sugar level sufficient to interfere with the normal functions of the nervous system and to lead to a variety of distressing symptoms such as apprehension, a feeling of insecurity, clouding of consciousness, loss of attention, aphasia, irritability and fatigue. In other words, the higher cortical functions may at times be disturbed leading to temporary abnormalities in impulse, temperament, character and intelligence. In addition, unpleasant neurologic signs may appear, ranging in their mild forms from diplopia, sweating and tremor to the more rare and severe types with convulsions and coma. The mild forms are extremely common and occur in many metabolic and endocrine disturbances. In fact, the symptoms often occur in the absence of any known disease process. Because such phenomena assume a leading place in the relationship of personality complaints to clinical practice, several examples are cited.

#### CASE REPORTS

A nurse, age 23, became apprehensive, tremulous and confused during her ward work at 11 A.M. Treat-

ment with sedatives gave no relief. The condition persisted for 6 months, leading to distress and worry as a consideration of changing her occupation. She was in the habit of eating a high carbohydrate-low protein breakfast at 7 A.M. Regulation of the diet to augment the protein intake at breakfast with a small carbohydrate supplementation at 10 A.M. controlled the symptoms and prevented the attacks.

A girl, age 12, experienced confusional states followed by fainting which usually occurred before noon on Sundays when she was in church. She was accused of malingering and dealt with severely by her parents. Breakfast on these days was unusually light and very early. The attacks promptly subsided when proper dietary steps were taken.

A physician's daughter, age 16, was brought in with a possible diagnosis of pituitary tumor because of ritual complaints during school at about 11 A.M. Several times a month she would be brought home, aphasic and put to bed without food because of nausea and headache (a frequent hypoglycemic symptom) until suppertime when, following eating, she would improve. As occurs so frequently, the episodes were aggravated during the week preceding menstruation. All symptoms were promptly and completely controlled with dietary regulation.

A dentist, age 36, developed a habit of avoiding difficult work between the hours of 10 A.M. and noon because he found the results to be of an inferior quality, and work done at such time frequently had to be repeated. He consulted several doctors and a psychiatrist. He abandoned smoking and relinquished some evening social activities, but to no avail. Here again dietary regulation solved the problem completely.

Relatively simple cases uncomplicated by concomitant clinical disease have been presented. They are characterized by: *a*) a predisposing type of dietary history, namely, high carbohydrate and low protein (or non-protein) meals, or long intervals between meals; *b*) evidence of autonomic vascular instability; *c*) failure to respond to sedation or other medication; *d*) cure by dietary means. All responded to an increased protein intake at meal time (at the expense of carbohydrate) plus the addition of a single small carbohydrate supplementation between meals. From the laboratory standpoint these cases are frequently obscured because the blood sugar at the time of complaint (as well as on the 4th and 5th hour of the glucose tolerance test) may be normal or at best only moderately depressed. The blood sugar does not fall to the low levels characteristic of hyperinsulinism in pancreatic adenoma.

In the excessive insulin sensitivity of some endocrine disorders (Simmonds' disease or Addison's disease) or as in liver disease. In contrast to this true organic hypoglycemic group, the cases here cited are described under the term of 'symptomatic hypoglycemia,' because the blood sugar values, at the time of complaint, cannot be demonstrated to be below the accepted normal. The phenomenon depends in final analysis less upon the level of the blood sugar than upon deficient carbohydrate oxidation in the central nervous system. This is in turn influenced by the adequacy or inadequacy of cerebral circulation, the oxygen supply, and the sensitivity of the various parts of the central nervous system itself both to diminished oxidation and to any compensatory adrenalin response. These factors account for the frequency of 'symptomatic hypoglycemia' in all clinical cases of neurovascular autonomic instability. The cases cited are but a few of many that we have seen. When uncorrected, the conditions may lead to distressing emotional and mental reactions which interfere with efficiency and produce anxiety states. The matter deserves far greater attention than it commonly receives in schools, colleges and factories where food consumption is hurried and inadequate, where hours are long, and emotional and mental tension runs high.

### *Psychogenic Mechanism*

The third fundamental mechanism of personality aberration is the psychogenic. In all such cases the mechanism is set in motion by an awareness of the problem, be it external (environmental) or internal, such as the knowledge of disease or bodily abnormality (somatic-psychic). Every disease process is accompanied or followed by some psychogenic reaction. The personality disturbance may be superficial and easily overcome by the correction of the disorder. It may become deep-seated into a pattern reaction or a personality habit that persists long after the exciting cause is withdrawn. It may become intense enough to obscure completely and over-shadow the precipitating etiology. It may even precipitate or act as the trigger mechanism in the production of a major psychosis.

Since bodily aberrations of which the patient is aware are common in endocrine practice, one might expect pronounced somatopsychic inferiorities. Such is indeed the case. The problems raised by obesity, hirsutism, hypogenitalism and dwarfism from the purely somatic angle demonstrate this well (2). One child may become extremely retiring and anti-social and the next one may compensate in the opposite direction. A somatopsychic mechanism of this type operating over a period of years, produces definite personality habits which may persist long after the original cause has been removed. One must not overlook that portion of the psychogenic mechanism caused by the environment. It usually consists of a long-standing psychologic problem of which the patient may or may not have been fully aware. The victim of his unsolved problems may not present any evidence of mental stress until a critical period in life when physical ill health precipitates some acute manifestation. For example, a woman who has been unhappy most of her life with an incompatible husband (environmental stress) turns to alcoholic excess at the time of menopause (added psychologic stress). It would be an easy matter to explain the situation in terms of menopause alone. Such an explanation, however, is not adequate. It was psychologic trauma of long-standing precipitated into an intolerable situation by a functional mechanism (menopause) which led her to attempt escape by the use of alcohol. In such cases proper estrogenic substitution may relieve the menopausal symptoms but will not get rid of the husband or control the alcoholism. However, a common-sense psychotherapeutic explanation of the entire mechanism may contribute further to a solution of the problem.

### SUMMARY

The triad of mechanisms, structural, functional and psychogenic, operate to produce personality changes. They may operate singly or more often in combination. Every medical case and particularly every endocrine case, presents problems in personality mixed with the medical story. They can almost invariably

be brought into the clear by skillful questioning. The personality factors may be represented only as a side issue or they may become the major complaints obscuring the entire clinical picture. Concomitantly with clarification of the medical aspects of any clinical, and particularly, any endocrine problem, it is essential to visualize the personality or behavior pattern in the light of the medical information

obtained. Medication alone does not solve these problems, nor does the application of popular psychologic formulation.

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# Furunculosis—Etiology and Treatment

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EVIDENCE indicates that there are many factors in the etiology of furunculosis. There seems to be a widespread belief among laymen that boils are the result of 'bad blood,' but no scientific support has been presented to substantiate such a view. Cleanliness of the skin was considered a major factor by Gant, Owens and Schwartz (1) in a severe outbreak of boils among a group of tunnel workers. The resistance of the host is an important factor in any infection and it seems logical to assume that low tissue resistance would play a rôle in the development of furunculosis. The present report reviews 16 cases in which tissue resistance seemed to be an important factor.

## METHODS

The 16 patients were college students between the ages of 17 and 25 years. They represented the only cases of furunculosis seen among approximately 2000 students over a period of one year. A careful history was taken and a physical examination made; particular attention was given to evidence of dietary deficiency. Hemoglobin was estimated by the Newcomber method. The basal metabolism was determined using the usual precautions and the new Sanborn waterless apparatus. Basal temperature was obtained by the method previously described in which the thermometer is left under the tongue for 10 minutes before the patient gets out of bed in the morning. Oral and rectal temperatures were taken at the time of examination.

## RESULTS

No correlation was apparent between the hemoglobin values and the development of boils. The average was 14.0 gm. of hemoglobin per 100 cc., the range 11.5 to 17.0 gm. Many

students free from boils have been seen in whom the hemoglobin values were in the lower part of this range. The largest boil observed in this group of patients was in the axilla of a boy whose hemoglobin was 15.3 gm.; the basal metabolic rate in this case was minus 24.

TABLE 1. BASAL TEMPERATURE AND B.M.R. IN  
16 CASES OF FURUNCULOSIS

Patient	Temperature		Sex
	°F.	B.M.R.	
MH	97.0	-12	M
JH	97.0	-24	M
DC	97.2	-19	M
BS	97.0	-20	M
CT	97.0	-19	M
MJ	97.4	-13	M
AG	97.5	-10	M
BS	97.0	-5	M
DC	97.5	-9	M
WS	97.5	+7	M
GJ	97.0	-20	M
JO	97.0	-15	M
DD	97.4	-9	F
GM	97.0	-15	F
AG	97.4		F
GM	97.2		F

The history and physical examination disclosed no evidence of malnutrition in this group of patients. There were no obvious local skin conditions contributing to the development of furunculosis. One factor was common in the physical examinations, namely, subnormal temperatures (table 1). Temperatures taken at the time of physical examination were unreliable since excitement or exercise will elevate the temperature. However, in most people with a subnormal temperature the rectal temperature is below 99.0° F. at the time of examination. Basal temperatures were uniformly low on this group of cases. The normal range for basal temperature is thought to be about 97.8 to 98.2° F.

The determinations of the basal metabolic rate were low, with one exception in which the reading was plus 7. However, in this case the body temperature was low and the high basal



metabolic rate was thought to result from nervousness and inability to relax. Most of the basal values were between minus 24 and minus 10 on the first test (table 1). It is thought that all cases would have been in this range if repeated determinations had been obtained. However, basal temperature is now being used as a criterion of lowered tissue resistance more than basal metabolism.

**Therapy.** The furuncles were given local treatment of heat and incision for drainage after pus was apparent. A few healed by resorption without being opened. Heat therapy consisted of hot wet dressings at home and 30 minutes to one hour under a Zeolite infra-red lamp at some time during the day at the Health Department.

Two cases served as controls without systemic therapy for 2 to 3 months. Boils recurred during this period; heat therapy was given as often as the time of these patients would permit but in each case the furuncle would enlarge and require incision. In one of the control cases thyroid therapy (1 grain a day) was started and heat therapy stopped when there were two tender lumps under one arm and one under the other. These were about half the size usually seen in this patient at the time of incision. Within 10 days the three tender lumps had completely disappeared, and no evidence of a recurrence has been observed. In the other control case thyroid therapy was started during a period of remission and no further furuncles appeared.

In the remaining 14 cases of furunculosis thyroid therapy was started when the patient was first seen. A second boil did not develop in any case during the period of thyroid therapy. One student who had repeated boils before therapy was started had no recurrences during 8 months of treatment. He then stopped medication without medical advice and boils recurred within two months. Details of the results with continued therapy have been published (2).

#### DISCUSSION

In the study of furunculosis in the present series it would seem that most of the usual etiologic factors, including cleanliness of the

skin, can be excluded. The low metabolic rate and subnormal temperatures indicate the tissue resistance might be low. Experimental it has been shown that skin disorders are numerous in the cretin rabbit (3). In cases of human myxedema the blood flow per minute and the skin temperature are markedly reduced and are promptly restored to normal during thyroid medication (4). Since the healing process is accompanied by an increase in circulation, it is not surprising that thyroid therapy would aid in skin infections in cases with poor peripheral circulation. Furthermore, it seems probable that an increased flow of blood through the skin would aid in the prevention of localized infection. The prompt response to thyroid therapy of the furuncles in this series of cases seems to furnish evidence for such a theory. The resistance of the skin to local infection seems to have improved since no more furuncles developed during the period of thyroid therapy. It is impossible to state whether the resistance was due to an action on the individual cells, to an increased blood flow, or to the combination of the two. Ball (5) reported that 'boils cleared with dramatic suddenness' using thyroid and potassium permanganate. It is impossible to state how much of the success with this therapy was due to both constituents but the same results have been obtained in the cases reported here with the use of thyroid alone.

#### SUMMARY

Furunculosis was observed in 16 patients. The basal metabolic rate or basal temperature was below normal in each case. Further lesions did not develop after starting thyroid therapy unless the medication was discontinued. It would appear that skin resistance may be a factor in furunculosis if the peripheral blood supply is below normal.

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## IN ANTI-THYROID PITUITARY HORMONE

IN HIS dependence upon the regulatory influences of the endocrine glands every human being is subject to two hazards. One is that his various endocrine structures will fail to rise to adequate heights of activity and the other is that they will become too active. When these possibilities are realized we have, on the one hand, such conditions as myxedema or simple menorrhoea and on the other hand, such disorders as exophthalmic goiter or von Recklinghausen's disease.

To the clinical endocrinologist, the second category of disorders is at least as impressive as the first, but laboratory investigators have in effect largely confined their attention to the first. This comes about perhaps because experimental animals seldom appear in the laboratories in a condition of glandular hyperactivity. It is customary, therefore, to think of problems of glandular control mostly in terms of presence or absence of stimulation. The general problem of why we do not all develop fatal exophthalmic goiter or other glandular hyperactivity early in life has received comparatively little explicit study. We are wont to think of the matter in about the same terms as those in which we regard the problem of control of the furnaces which heat our homes. When more heat is desired the drafts are opened and the fire burns more briskly. When the rooms become too warm the drafts are closed and the fire dies down. It is only when a conflagration breaks out that positive measures for the lessening of combustion are invoked. The possibility that the glands may be under positive inhibitory as well as stimulative control has received relatively little consideration at the hands of investigators.

In the case of nervous control of body functions, on the other hand, the possibilities of positive and of negative control have been well explored, and the principle of reciprocal innervation has been well established. Thus dilatation of the pupils may be brought about either by stimulation of dilator mechanisms or by inhibition of constrictor mechanisms. Similarly, a rapid pulse may be evoked either by augmented activity of the sympathetic innervation or by depression of the vagus mechanism.

In a recent publication from the Institute of Physiology of the University of Buenos Aires, Reforzo-Membrives<sup>1</sup> has approached the problem of thyroid control in terms of inhibition rather than of stimulation. The strategy of his study was based on the fact that the anterior pituitary of the rat exerts a strong thyroid-stimulating action and the thyroid of that animal is highly resistant to such stimulation whereas the thyroid of the guinea pig is very sensitive to the action of thyrotropic hormone. By utilizing both species jointly in the research it was possible to exploit both the high efficiency of a donor gland and the high sensitivity of a recipient organ.

To adult male rats desiccated thyroid substance was given in daily dosage of 50 to 100 mg. for periods of 22 to 32 days. The hypophyses of the treated rats were then administered intraperitoneally in saline-fluid suspension to young guinea pigs. Usually 2 glands were given on each of 2 successive days. The results of the treatment were then determined, using three criteria: the thyroid glands of the recipient animals were studied histologically, the oxidizing power of the same glands was determined, and the basal metabolic rates of the treated guinea pigs were investigated. The studies were controlled by the use of hypophyses from rats kept on standard diets without the thyroid administration.

It was found, in brief, that when normal rat hypophyses were injected, the expected thyrotropic influences appeared. The thyroids of the treated guinea pigs were 35 per cent *heavier* than those of untreated animals and showed the typical picture of hyperfunction. But when the hypophyses of thyroidized rats were used, the opposite sort of effects was noted. The thyroids of the recipients were 26 per cent *lighter* than normal and showed a corresponding reduction in the height of the thyroid epithelium. Similarly in the first case the oxidation index of the recipient thyroids was 28 per cent augmented while in the second case it was 23 per cent decreased. Finally, the basal metabolic rate of the guinea

<sup>1</sup> REFORZO-MEMBRIVES, J.: Thyroid-inhibiting action of the hypophyses of rats fed with thyroid. *Endocrinology* 32: 263, 1943.

pigs was augmented from 9 to 25 per cent by the normal rat hypophyses but depressed from 26 to 48 per cent by the hypophyses of thyroidized rats. In control experiments in which tissues other than the hypophyses of such rats were administered, the thyroids of the recipient animals were not significantly affected.

The evidence thus seems clear that when the organism is subjected to hormone over-stimulation not only may there be a depression of autogenous hormone which would exaggerate the functional pathology but also secretion of a positive antidoting hormone. These new findings supplement in a meaningful way the older observations that gland deprivation results in the augmentation of compensatory stimulating hormone as is seen, for example, when the hypophyses of castrated animals secrete excessive amounts of gonadotropic hormone. Thus a principle of reciprocal hormonal control comparable with that of reciprocal innervation is exemplified. A research investigation of such fundamental significance will no doubt stimulate similar studies in other laboratories and with other species.

The findings of Reforzo-Membrives offer a

suggestion as to how iodine, which primarily augments thyroid secretion, can be effective in mitigating the symptoms of exophthalmic goiter—a paradox that has long demanded elucidation. Possibly the iodine administration results, directly or indirectly, as does thyroid administration, in the production of hypophyseal antithyroid hormone. It may be that it is the pituitary hormone which was, in whole or in part, the effective agent in the 'anti-thyroid serum' of older investigators and in animals 'immunized' by thyroglobulin as recently studied by Lerman.<sup>2</sup>

The demonstration of a specific depressant hormone in case of thyroid-treated rats demands further search for similar agents in other cases of induced or clinical conditions of hyperhormonization. Should a principle comparable to reciprocal innervation prove to be of general occurrence in our field, endocrine theory would be fundamentally enriched and a way might be opened for an effective extension of the possibilities of hormone therapy.

R.G.H.

<sup>2</sup> LERMAN, J.: Endocrine action of thyroglobulin antibodies. *Endocrinology* 31: 558. 1942.



# CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, W. EVERETT, MURRAY B. GORDON, R. H. GREENBLATT, E. C. HAMBLIN, CHARLES W. HOOKER, R. G. HOSKINS, E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, C. C. PFEIFFER, J. P. PRATT, E. C. REIFENSTEIN, RUS B. RUBENSTEIN, PATRICIA H. SMITH, EMMERICH VON HAAM, HAROLD WOOSTER.

## BOOK REVIEWS

The Biological Action of the Vitamins. A Symposium. Ed., E. A. Evans, The University of Chicago Press, Chicago, Ill. 1942.

The hormones and the vitamins, although separately categorized, are biological regulators of a similar order. Both have important influences on cellular metabolism and deficiencies both are manifested in subtle changes in nutrition as well as in physiological functions. Both likewise are characterized by remarkable potency, functioning perhaps in all cases as catalysts or components of catalytic systems. The interrelations of the vitamins and the hormones are increasingly engaging the interests of investigators. Although this book is not primarily concerned with the hormones it will be of interest to endocrinologists who are concerned with underlying biology.

The first article, by C. A. Elvehjem deals with the biological action of the vitamins. It is in the nature of a historical introduction. It includes a section on the functional relations of the vitamins and the hormones. This is followed by a discussion of vitamins and enzymes and their interrelationships.

Thirteen other chapters by outstanding investigators deal with coarboxylase, vitamin B<sub>1</sub>, riboflavin, nicotinic acid, pyridoxine, pantoic acid, biotin, choline, the economy of phosphorus, and vitamin K. The chemical, biological and clinical aspects of each are considered. The book is readable, authoritative and relatively comprehensive. It can be highly recommended to non-specialists seeking fairly easy orientation in the field.—R.G.H.

## ADRENALS

LINTON, M., AND G. W. THORN.

The effect of 11-desoxy-17 hydroxycorticosterone on renal excretion of electrolytes

*Science* 96: 343. 1942.

Results of injection of a normal dog with 11-desoxy-17 hydroxycorticosterone showed that it belonged to the group of compounds possessing "Na and Cl-retaining" property. Addition of a hydroxyl group on C<sub>17</sub> to desoxycorticosterone resulted in formation of a compound with lower sodium and chloride-retaining properties, but similar addition to corticosterone resulted in formation of a compound which facilitated Na and Cl excretion.—*Courtesy Biol. Abst.*

ENGEL, F. L., W. H. MENCHER AND G. L. ENGEL.

"Epinephrine shock" as a manifestation of a pheochromocytoma of the adrenal medulla. Report of a case with successful removal of the tumor. *Am. J. M. Sc.* 204: 649. 1942.

The successful removal of an adrenal medullary pheochromocytoma in a 23 year old woman is recorded. Symptoms resembling epinephrine shock had been present in increasing severity for 2½ years. Shock attacks were precipitated by any stimulus which elicited sympathetic discharge. Postoperatively the patient developed a transient postural hypotension and a low sugar tolerance curve with hypoglycemia.—C.P.

HOFFMAN, W. C., R. A. LEWIS AND G. W. THORN.

The electro-encephalogram in Addison's disease. *Bull. Johns Hopkins Hosp.* 70: 335. 1942.

Abnormalities in the resting pattern of EEG and increased sensitivity of EEG to voluntary hyperventilation observed in high proportion of patients with Addison's disease, are unaffected by desoxycorticosterone acetate. Adrenal cortical extract and intravenous glucose in some instances reduced cortical sensitivity to hyperventilation.—D.A.M.

pigs was augmented from 9 to 25 per cent by the normal rat hypophyses but depressed from 26 to 48 per cent by the hypophyses of thyroidized rats. In control experiments in which tissues other than the hypophyses of such rats were administered, the thyroids of the recipient animals were not significantly affected.

The evidence thus seems clear that when the organism is subjected to hormone over-stimulation not only may there be a depression of auto-genous hormone which would exaggerate the functional pathology but also secretion of a positive antidoting hormone. These new findings supplement in a meaningful way the older observations that gland deprivation results in the augmentation of compensatory stimulating hormone as is seen, for example, when the hypophyses of castrated animals secrete excessive amounts of gonadotropic hormone. Thus a principle of reciprocal hormonal control comparable with that of reciprocal innervation is exemplified. A research investigation of such fundamental significance will no doubt stimulate similar studies in other laboratories and with other species.

The findings of Reforzo-Membrives offer a

suggestion as to how iodine, which prima augments thyroid secretion, can be effective mitigating the symptoms of exophthalmic go—a paradox that has long demanded elucidation. Possibly the iodine administration results, directly or indirectly, as does thyroid administration, in the production of hypophyseal anterior pituitary hormone. It may be that it is this pituitary hormone which was, in whole or part, the effective agent in the 'anti-thyroid serum' of older investigators and in animals 'immunized' by thyroglobulin as recently studied by Lerman.<sup>2</sup>

The demonstration of a specific depressive hormone in case of thyroid-treated rats demands further search for similar agents in other cases induced or clinical conditions of hyperhormonalization. Should a principle comparable to reciprocal innervation prove to be of general occurrence in our field, endocrine theory would be fundamentally enriched and a way might be opened for an effective extension of the possibilities of hormone therapy.

R.G.H.

<sup>2</sup> LERMAN, J.: Endocrine action of thyroglobulin antibodies. *Endocrinology* 31: 558. 1942.



otic fibrous dysplasia. The outstanding features of the syndrome are multiple osseous lesions associated with endocrinological disturbances of various types but usually with skeletal precocity; and some have sexual precocity, features suggesting thyroid disorders and acromegalic changes. Starches of cutaneous pigmentation are also characteristic of the disease. In the 2 patients the authors report there were also present visual changes, apparently due to the great bony overgrowth of the base of the skull pressing on the optic nerves and, in one instance, encroaching on the orbit. In 1 patient also the serum calcium was reported elevated to 12.6 mgm.%, the phosphate lowered to 2.6 mgm.% and serum phosphatase high at 30 Kay units. They stressed the absence of osteoclastic foci, which was also stressed by Albright et al., and believed the pathologic picture to be due to collagenous osteogenesis of the marrow with attritive osteolysis of the medullary trabeculae.—*J.E.H.*

HARRISON, F. G.

Urinary obstruction in children inducing renal hyperparathyroidism. *J. Urol.* 48: 44. 1942.

Urinary obstruction with imposed infection reduces renal insufficiency and induced hyperparathyroidism with or without rickets, dwarfism and infantilism being present. 5 cases are presented with mortality in 2. Of 3 postoperative cases, 2 are free of infection and have resumed growth; one has a guarded prognosis with a single kidney and infection. Prognosis in such cases is poor unless treatment is established before renal insufficiency has progressed.—*J.A.M.*

ULIAN, O. C., D. E. CLARK, J. VAN PROHASKA, C. VERMEULEN AND L. R. DRAGSTEDT.

The antagonistic effect of lipocaic and the anterior pituitary on fat metabolism. *Am. J. Physiol.* 123: 264. 1943.

Lipocaic, the factor of the pancreas that prevents deposition of fat in the liver of the depancreatized dog, inhibits the accumulation of fat in the livers of guinea pigs injected with the ketogenic factor of the pituitary gland. Fatty livers observed in the "Houssay animal" are also prevented by lipocaic. The results imply that lipocaic is antagonistic to the fat metabolism factor of the pituitary gland and causes migration of fat to the body depots. However, factors other than the ketogenic hormone of the pituitary gland are likewise involved in fatty infiltration

of the liver and are also controlled by the lipocaic activity of the pancreas.—*R.B.G.*

LAWRENCE, R. D., A. MEYER AND S. NEVIN.

The pathological changes in the brain in fatal hypoglycaemia. *Quart. J. Med.* 11: 181. 1942.

The authors briefly review the literature on fatal hypoglycemia and the various conceptions which have been proposed as to the cause of death in this condition. They report 6 cases of their own with fatality resulting from hypoglycemia. Two of these were diabetic patients whose hypoglycemia resulted from inadvertent administration of too great an amount of insulin; 1 patient suffered his hypoglycemia from an unrecognized islet cell adenoma; the other 3 were given insulin shock therapy for mental disorders. The most characteristic pathologic feature of the condition is the widespread degeneration and disappearance of the nerve cells in the cerebral cortex, basal ganglia and cerebellum, especially noteworthy and constant being the changes in the caudate nucleus and putamen. They point out the lack of evidence that insulin has any direct effect on the vasomotor regulation of the brain. They feel that the most likely explanation for the mechanism of the hypoglycemic changes is due to the inability of brain tissue to use any other substrate than glucose for its oxidative processes. Absence of glucose thus means "suspension of vital metabolism which, if prolonged, must lead to death and irreversible lesions in the nervous tissue." The more prolonged the coma from hypoglycemia, the more likely the fatal termination. They also point out that it is incorrect to describe this reaction as anoxia and suggest a new term—oxyachrestia (cf. achrestic anemia, from *χρησις*=use).—*J.E.H.*

MOORE, T. V.

Physiological factors in the treatment of mental disorders. *Psychiat. Quart.* 16: 765. 1942.

The author treated a series of patients presenting in general manic depressive symptoms with an extract of adrenal cortex and a number of schizophrenic patients with anterior pituitary-like substance. The manic depressive patients received one cc. of eschatin 3 times a week, the schizophrenic patients 250 units of follutein 3 times a week. The initial dose of follutein was usually 125 units. After a course of 15 to 20 injections, a new series was started after an interval of a week to 10 days. Five or more series were

given according to the circumstances. Eschatin was supplemented by ascorbic acid, 100 mg. tablet, t.i.d., a.c. Follutein was supplemented by thiamin hydrochloride in the same dosage. There is some weak evidence to show that the treatment of the dementia praecox patients was beneficial, but rather strong evidence that the conditions of the manic-depressives were distinctly ameliorated. The efficacy of the treatment was tested by the comparison of a treated series of hospital patients (24 cases) with an older series (48 cases) of untreated hospital patients. The critical ratio of the difference in the percentage of recoveries in the 2 series was 4.62, which suggests that for some reason other than chance the treated series had a much more definite trend to recovery. Of the untreated patients, 8.3% and of the treated, 58.3% were discharged from the hospital in less than 6 months. Besides the hospital cases 23 ambulant patients were treated, with 69.6% of apparent recoveries. The author feels that this type of therapy merits further trial.—From "*Hartford Abstracts*."—R.G.H.

#### SELYE, H.

Production of nephrosclerosis by overdosage with desoxycorticosterone acetate. *Canad. M. A. J.* 47: 515. 1942.

In 12 3-day-old White Leghorn chicks, the author gave daily 0.5 mgm. desoxycorticosterone acetate in oil subcutaneously. Controls were treated with similar doses of cholesterol. After 10 days it was obvious that the D.C.A.-treated birds were consuming more water and developing edema. All the birds were killed at the 20th day. Organs of the control group were normal. The treated birds showed signs of fluid retention with ascites, pericardial effusion and the subcutaneous tissues were edematous. Gonads in both sexes showed marked distension with edema. The hearts were enlarged, partially due to hypertrophy and partially to dilatation. Blood vessels were thickened. The kidneys were considerably enlarged and were grayish and swollen. The tubules had distended lumens. There was cloudy swelling in all segments of the nephron down to the collecting tubules. The entire parenchyma showed hyperaemia and the glomeruli were enormously enlarged. The NPN did not seem to be raised despite marked renal lesions. The blood sugar, however, was increased in the treated ones. The possible significance of these observations relative to the pathogenesis of hypertension and nephrosclerosis in man is discussed.—J.E.H.

#### SELYE, HANS, AND S. ALBERT.

Morphogenetic actions of various steroids in the castrate male rat. *J. Pharmacol. and Exper. Therap.* 76: 137. 1942.

The various steroids stimulate the male accessory sex organs in a selective manner. Testosterone stimulates predominately the seminal vesicles, androsterone the prostate, and androstenediol the preputial glands. Kendall's Compound "E" has a definite prostate stimulating activity. Progesterone and pregnenolone have no seminal vesicle stimulating action in castrates. Desoxycorticosterone is without stimulant activity and appears to have inhibiting action due to the atrophy of the adrenal cortex.—C.P.

#### WILLIAMS, E. H., AND C. A. WRIGHT.

Clinical studies of endocrine dosage in the treatment of involutional psychoses. *M. Rec.* 155: 11. 1942.

Eleven cases were treated successfully and without recurrence for at least one year. Treatment consisted of 10,000 rat units  $\alpha$ -estradiol benzoate one to three times a week for several weeks or until mental symptoms and general physical condition approached normal. Concurrent use of sedatives was limited to small doses. Authors call attention to importance of adequate dosage in treatment of this condition.—D.A.M.

#### ZEIFERT, MARK.

Massive dose testosterone therapy in male involutional psychosis. *Psychiat. Quart.* 16: 319. 1942.

Five patients were treated with high doses of testosterone propionate, 25 mg. twice daily, one course amounting to at least 1300 mg. over 40 days. Elimination of suggestion was attempted. Only in one case control with sterile water is reported. No urine assays were done. Erections and rare ejaculations occurred, but no priapism was noted. Psychologically: 2 cases were scarcely influenced, 1 showed improvement lasting 2 months, 2 patients improved and have been adjusting outside since 1940. The author attributes the improvement to the hormone therapy.—*Courtesy Biol. Abst.*

#### ZONDEK, B., AND Y. M. BROMBERG.

Autodetoxication of stilbestrol during pregnancy. *Lancet* 1: 381. 1942.

Clinical observations on 4 women showed that during pregnancy and the puerperium, women

can tolerate very large doses (270-445 mg.) of diethylstilbestrol dipropionate without developing side-effects. The same patients some months after childbirth showed severe toxic manifestations with only 2-5 mg. doses indicating that detoxification of diethylstilbestrol takes place during pregnancy.—*D.A.M.*

## GONADS

ALBRIGHT, F., P. H. SMITH AND R. FRASER.

A syndrome characterized by primary ovarian insufficiency and decreased stature. Report of 11 cases with a digression on hormonal control of axillary and pubic hair. *Am. J. M. Sc.* 204: 625. 1942.

Eleven cases are presented as a new clinical syndrome from life-long ovarian insufficiency. The syndrome is characterized by infantile sexual organs, lack of breast development, sparse axillary and pubic hair, short stature, congenital anomalies, late closure of the epiphyses, precocious senility, excess urinary excretion of follicle-stimulating hormone and a decrease but not an absence of urinary excretion of the 17-keto steroids. The syndrome must be differentiated from other conditions causing primary amenorrhea, namely panhypopituitarism, "premenstrual menopause praecox" and a selective deficiency of the gonadotropic hormones of the anterior pituitary. The criteria for this differentiation are outlined. The author suggests that the lack of hair is due to deficiency of the adrenal cortical hormone. Replacement therapy with estrin leads to marked amelioration of the syndrome.—*C.P.*

BISCHOFF, F., AND G. J. CLARKE.

Influence of nephrectomy on ovarian response to gonadotropins. *Am. J. Physiol.* 138: 241. 1943.

Three gonadotropic preparations, sheep pituitary gonadotropin, pregnant mare serum and pregnancy urine extract, were tested in the partially nephrectomized 22 day old female rat. The sheep gonadotropin, when administered in doses non-stimulating to the intact animal, produced an increase in ovarian weight in the operated littermate. Although augmented ovarian response to pregnant mare serum was noted in the partially nephrectomized rat, the results could be accounted for by the body weight difference between the operated and intact control groups. Pregnancy urine extracts administered in three

different doses produced significantly heavier ovaries in the operated rat than in the littermate control. The absolute increase in ovarian weight averaged approximately the same for each dose level covering an eightfold dosage range.—*R.B.G.*

HAMILTON, JAMES.

Male hormone stimulation is prerequisite and an incitant in common baldness. *Am. J. Anat.* 71: 451. 1942.

The etiology of common baldness was studied experimentally in men with testicular insufficiency, namely: 10 eunuchoids; 94 eunuchs, 10 of whom had been castrated prepubertally, 34 bilaterally orchidextomized during adolescence, and 50 castrated as adults. Common baldness never appeared in the 54 men who did not mature sexually. This is scarcely fortuitous in view of the genetic predisposition to alopecia in some of these men as indicated by tendencies to become bald when provided with exogenous androgens and loss in normal men, 43% according to Snyder and Yingling. Concomitantly the amounts of dandruff and sebaceous secretion were less in castrates than in normal men. Male hormone treatment of 12 of these castrate and eunuchoid men, providing stimulation considered equivalent to that in normal men, resulted in increased sebaceous secretions, acne and dandruff, and 4 instances of baldness in a pattern observed in normal men. Progressive loss of head hair ceased when androgenic medication was discontinued in 2 cases, recommenced upon further therapy. Castration of men becoming bald prevented progression of alopecia but promoted no general regrowth of hair on bald areas. Pedigrees of patients receiving testosterone compounds, suggest that a genetic predisposition and male hormone stimulation are necessary to development of common baldness.—*Author's Summary.*

JONES, G. E. S., AND R. W. TE LINDE.

An evaluation of progesterone therapy in treatment of endometrial hyperplasia. *Bull. Johns Hopkins Hosp.* 71: 282. 1942.

Of 28 cases of functional uterine bleeding associated with pathological picture of endometrial hyperplasia treated with progesterone, only 2 required radical procedures. Reduction of incidence of hysterectomy and irradiation therapy from 37 to 7% by use of progesterone indicated value of therapy. Dosage of progesterone and time interval of administration is discussed.—*D.A.M.*



KAHLE, P. J., H. D. OGDEN, JR., AND P. L. GETZOFF.

Effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. I. Clinical observations. *J. Urol.* 48: 83. 1942.

Seven cases of adenocarcinoma of the prostate, 6 proven by biopsy, were treated for 2 years with diethylstilbestrol and diethylstilbestrol dipropionate in doses averaging 5 mg. intramuscularly, three times a week. Treatment in all cases has afforded prompt relief of pain and urinary symptoms with general improvement in health. Regression of lesion has occurred in all patients and have lost their malignant characteristics as judged by rectal palpation. Clinical improvement is associated with regression of metastatic lesions to bones and lymph nodes. No side effects of treatment were encountered except for a transient gynecomastia in one patient.—*D.A.M.*

SCHENKEN, J. R., E. L. BURNS AND P. J. KAHLE.

Effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. II. Cytological changes following treatment. *J. Urol.* 48: 99. 1942.

See abstract above. Regressive nuclear and cytoplasmic changes occurred in neoplastic cells of all cases. Nuclei showed reduction in size, condensation of chromatin, loss of nucleoli and mitotic figures and pyknosis. Nuclear diameters diminished by 18–56% during treatment. Regressive cytoplasmic changes consisted of appearance of vacuoles, displacement of nuclei toward lumen of acinus, rupture of cell membranes and coalescence of vacuoles.—*D.A.M.*

KEARNS, W. M.

Treatment of carcinoma of the prostate with estrogens. *Wisconsin M. J.* 41: 575. 1942.

Thirty-seven patients ranging from 48 to 86 years (average 67) were treated. Seven died during treatment, 5 of intercurrent causes and 2 in which progress of the carcinoma appeared to be the cause. The estrogen, diethylstilbestrol was administered orally in 1 mg. doses, three times a day for 2 to 3 weeks, the dosage then being reduced to 2 mg. daily for 2 to 4 weeks, and then decreased to 1 mg. daily indefinitely. Clinical improvement was evidenced by gain in weight, usually relief from pain throughout the body, improvement in blood count, slowing of sedimentation rates and an approach to normal

in phosphatase estimation. After 4–5 months skeletal roentgenograms improved. The prostate decreased in size and lost its dense nodularity, fixation and indiscrete outline. Gastric and breast stimulation irritation developed in several of the patients and in the recent treatment ethinyl estradiol was substituted for diethylstilbestrol using .05 mg. doses. Several patients were implanted with two 10 mg. pellets of estradiol or two 15 mg. pellets of estradiol benzoate once monthly. Gastric irritation is avoided by this procedure. Administration of estrogen is considered of preference to castration.—*D.A.M.*

MILLER, MARY L.

Neutral steroids in the urine of individuals with benign hypertrophy of the prostate. *J. Urol.* 47: 846. 1942.

Androsterone, trans-dehydroandrosterone (isolated as 3-chloro- $\Delta^5$ -androstene-17) and cholesterol were isolated from neutral steroid fraction of urine of patients with benign prostatic hypertrophy. Comparison of values for normal men and eunuchs indicated somewhat smaller amounts of androsterone but no significant difference for trans-dehydroandrosterone. There was no evidence for the occurrence of abnormal hormone.—*D.A.M.*

MILLER, MARY L., AND R. A. MOORE.

Variation in the daily urinary excretion of androgens in relation to benign hypertrophy of the prostate. *J. Urol.* 48: 544. 1942.

Daily variation in urinary androgen was measured for a period of 30 days in 4 men, ages 73 to 81, 2 men with benign hypertrophy and two of comparable age without prostatic hypertrophy. Daily fluctuations in the two persons with hypertrophy were no greater than in the two without.—*D.A.M.*

NEWERLA, G. J.

The history of the discovery and isolation of the male hormone. *New England J. Med.* 228: 39. 1943.

The history of the discovery and isolation of the androgenic principle of testes is traced. An interesting chronological tabulation and an excellent bibliography are appended.—*R.B.G.*

SELYE, HANS, AND S. ALBERT.

The effect of various steroids in intact male rats. *Am. J. M. Sc.* 204: 876. 1942.

All hormonally active steroids (whether the

the folliculoid, testoid, luteoid, corticoid, or permatogenic) cause involution of the Leydig cells of the testis. Of these the folliculoids are the most active on a dosage basis. The Leydig cell involution does not result from the direct steroid action but due to the inhibition of the pituitary gonadotropic hormone inhibition the action of the steroids on the structural appearance of numerous other organs has also been tabulated.—C P

SIMON, S M., AND A F ULLMAN

A clinical study of 105 patients treated with estrogen and progesterone *Connecticut State M J* 6 921 1942

Eighty one menopausal patients, natural, surgical and irradiated, were treated once weekly with estradiol dipropionate in doses of 1 mg for the first week or two followed by 0.2 mg doses for a total period of 5 or 6 weeks. This was followed by intervals between treatment of 2-4 weeks depending on relief of symptoms. Thirty-nine of the patients received thyroid and sedatives in addition to estrogen therapy. Sixty or 62% of patients had excellent or adequate results, 22 or 27% inadequate and 9 or 11% had no relief. Colored patients seem to respond more favorably than white. Twelve cases of oligomenorrhea treated with estradiol dipropionate (total dose 5 mg) for 3 weeks followed by progesterone (total dose 6 mg) for one week. The series was then repeated for an average of 3 months. In 10 or the 12 patients, a normal menstrual flow lasting for several months was attained. Eight cases of secondary amenorrhea also treated with estradiol dipropionate and progesterone yielded only 3 satisfactory results. Three patients with juvenile menorrhagia were relieved and their menstrual cycles completely regulated with progesterone.—D A M

## HYPOPHYSIS

ANDERSON, J A., AND W. R. MURLIN

Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus *J Pediat* 21 326 1942

The physiological antagonistic action of adrenal cortical extract in pitressin on the excretion of sodium, chloride and water was confirmed in the human subject with diabetes insipidus. Cortical extract fails to increase potassium excretion unless pitressin is supplied. It is suggested that facultative reabsorption of water as induced by

pitressin must be in progress before kidney tubules can selectively excrete sodium and potassium.—D A M

## PANCREAS

ALTSCHUL, A., AND A NATHAN

Diabetes mellitus in Harlem Hospital outpatient department in New York. A comparison of certain etiologic factors in Negro and white patients *Jour Am Med Assoc* 119 248 1942

The number of new and referred diabetic patients at the Harlem Hospital outpatient department increased 2½ times in the 1935-39 period. In 7 years the mortality increased 76% for Negro as compared with 26% for white diabetic patients. The onset of diabetes was much earlier in the female Negro than in the female white patient. Heredity and familial incidence were factors in the Negro diabetic etiology. Obesity was equally common in both Negro and white female patients. Undernutrition was slightly higher in the Negro than in the white groups. The Negroes had higher per cent in the mild diabetic group than did whites.—Courtesy *Biol Abstrs*

ANDERSON, G E

Problem of retinitis in the diabetic patient *Arch Ophthalm* 28 679 1942

Present-day orthodox treatment of diabetes mellitus has been disappointing in so far as it concerns the prevention of premature arteriosclerosis in general and diabetic retinitis in particular. There seems to be a relationship between the development of fatty infiltration of the liver and a similar process in the arteries—so universal in all diabetics of long duration. Both of these processes are intimately related to faulty fat metabolism. The diabetic should be kept from obligatory fat metabolism by forced carbohydrate and protein metabolism by means of diets relatively high in both moieties and low in fat, together with adequate insulin. Weight loss in the arteriosclerotic diabetic is to be meticulously avoided since it invites unnecessary fat mobilization from the fat depots and amounts to the equivalent of a high fat diet. Conventional normal readings for blood sugar are not physiologic for the arteriosclerotic diabetic. Their maintenance not infrequently invites relative hypoglycemic states to which there is compensatory suprarenal response and secondary hyper-

in whom the stimulus to thyroid overaction is unusually powerful or persistent. The occasional simultaneous development of exophthalmos and localized pretibial myxedema could be explained by such a hypothesis."—*J.E.H.*

TROTTER, W. R. AND N. WALLACE.

Thyroxine as a practical treatment of myxedema. *Brit. M. J.* 1: 183. 1942.

A typical case of myxedema is described. The patient reacted to the oral administration of thyroid with vomiting, edema of the face and pains in the limbs. Thyroxin was administered intravenously with good therapeutic results; the maintenance dose was found to be 7.5 mg. given in a single injection once every four weeks.—*E.B.A.*

WATSON, C. J., D. CRAIG AND N. BEACH.

Myxedematous ascites. *Internat. Clin.* 4: 177. 1941.

This is a brief discussion of the subject with an illustrative case reported in detail. In 1 of these hydrothorax occurred, but this is not believed to be due to the myxedema. Ascites without heart failure occurs in myxedema only occasionally. Of 22 cases of myxedema, observed over a period of 20 years, but 2 cases of this type were observed. The presence of mucin in the ascetic fluid in myxedema indicates that the ascites is directly related to the underlying cellular disturbance of the disease, i.e., elaboration of an abnormal fluid rich in mucin.—*I.B.*



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## Familial Eunuchoid Gigantism

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THE USUAL classification of giants differentiates between the so-called normal giants and true endocrine giants. The normal giants are tall men, often with tall forearms, with normal sexual development and normal hair growth in whom procreative ability is not known to be impaired. Examples of this type of overgrowth are Falta's (1) giant and Carnera, the boxer. Even in individuals who have been classified as normal giants there are usually the stigmata of hyperpituitarism evident from prognathism, wide spacing of teeth and very large hands and feet. Since, as far as we know at present, growth in length of long bones is dependent upon a stimulus from the anterior lobe of the hypophysis, it is evident that whatever the classification is, abundant or excessive pituitary stimulus must be present in every case of abnormal height.

Familial gigantism has seldom been recorded. Davenport (2) in his studies on inheritance of stature has collected data on a few families with tall members. His conclusions are as follows:

Assuming that excessively tall stature is the result of excessive activity of the pituitary gland, then it seems necessary to conclude that peculiarities in the functioning of endocrine glands are influenced by genetic factors—have an inheritable basis.

Unique in medical history perhaps is the record of the Minneapolis giant, described by Gray (3). His paternal grandfather, the Norwegian giant, was reported to have been 8 ft. 4 in. Both parents were more than 6 feet tall. The giant himself was 7 feet tall. It would appear that the familial and hereditary influence must have been important in this family, also that the disturbance of sexual function must have been only partial. And yet, the picture of the Minneapolis giant is one of advanced hyperpituitarism. The dividing line therefore between so-called normal giants and those due to abnormal pituitary function is at best a vague one.

Pituitary gigantism is considered to be secondary to pituitary tumors. We know that in the closely related acromegaly eosinophilic tumors of the hypophysis have been present in nearly half of the cases which have come to

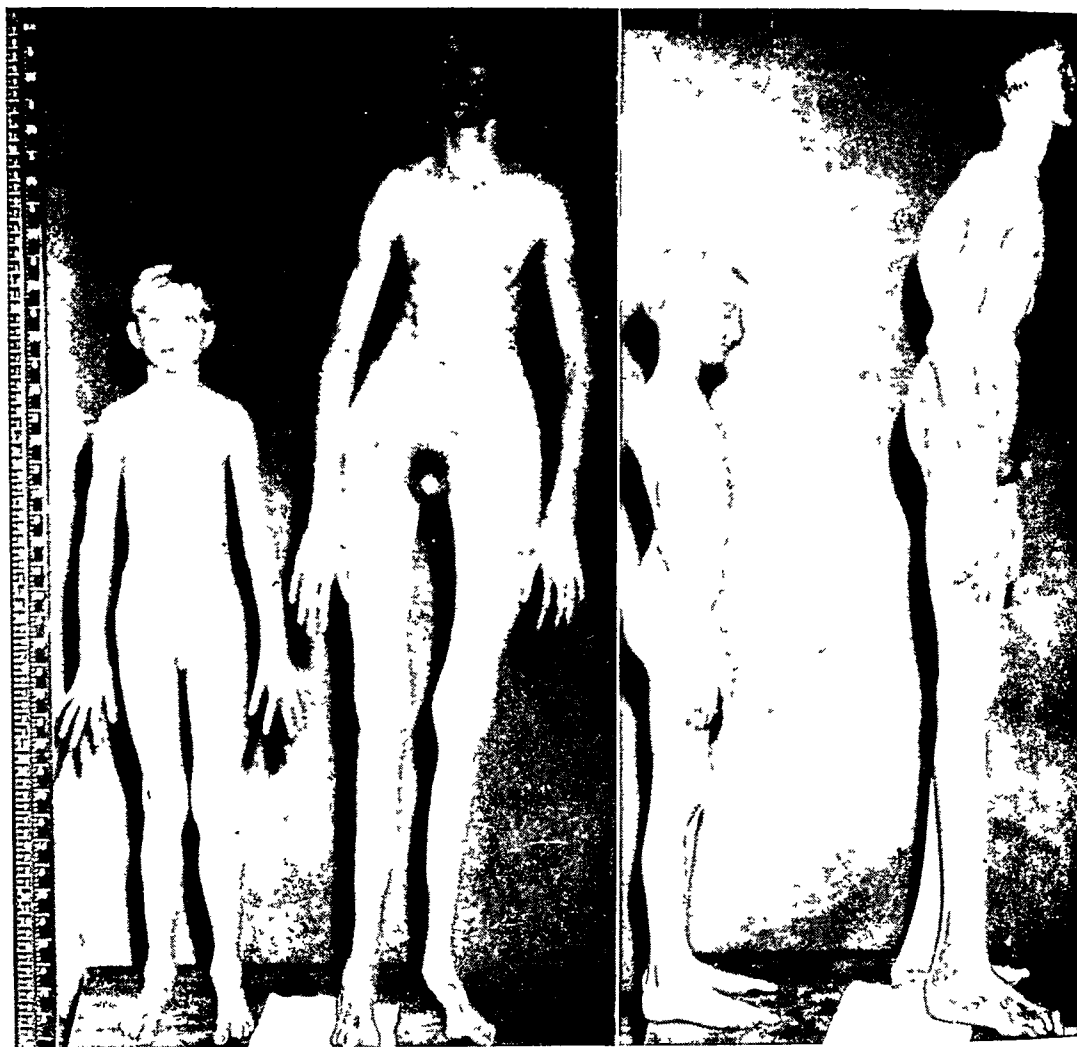


FIG. 1. Brothers, Raymond and Lawrence D., aged 10 and 19 years, respectively. Raymond was 9 inches taller than average for his age. Note the length of the foot and great toe in photograph on the right. Lawrence was 6 ft. 11 in. tall. Note the size and shape of the hands.

operation or autopsy. Atkinson (4) who collected the cases described from 1935 to 1937 found in 287 cases the occurrence of adenomata in 124 in which the condition of the pituitary gland is reported. It is reasonable to suppose that in gigantism the same may be true in cases which reveal signs of definite hyperpituitarism. The pathologic data on giants are, however, deplorably meager.

The last group are the eunuchoid giants in whom for one reason or another the testes or ovaries develop late or are atrophic or destroyed. The physical status of such patients is very characteristic and consists of absence of secondary sex characteristics, hypotrichosis and impotence, combined with overgrowth of long bones and open epiphyses.

We have had the privilege of studying for

several years a patient with typical eunuchoid gigantism.

#### CASE REPORT

The patient, *Lawrence D.*, was sent to Barnes Hospital from Barnard Skin and Cancer Hospital for study of the etiology and nature of his excessive height. He went to the Barnard Hospital because of an ulcer on his leg, which on admission was still present. The family history will be revealed later. He had the usual children's diseases: measles, mumps, whooping cough, and chicken-pox. At the age of 4 or 5 years his unusual height was discovered. When he started to school at the age of 7, no one would believe that he was only 7 but rather thought that he was about 9 years old. He was always the tallest boy in his class and far above the average height. He made average marks in school. At the age of 12 years he was 5 ft. 10 in.; at 16 he was 6 ft. 1 in., at 18, 6 ft. 5 in., and at the time of admission 6 ft. 11 in. tall.

In 1933 he entered another hospital because of a

descended left testicle. During his stay in the hospital a kidney infection was discovered and treated. He had never received specific treatment for the undescended testicle, nor for the apparent eunuchoidism which accompanied it. Five months before he entered Barnes Hospital he accidentally struck the inside of his left foot with the shoe of the other foot. Since then there has been an ulcer of the right foot which has caused him to give up his occupation in a printing office, where he was running a press. He never complained of headaches. After long reading he has some blurring of vision. There are no signs of diabetes insipidus. He has very little sexual desire.

Physical examination revealed a very tall young man, 19 years old, whose appearance is best shown by the photograph. The size and shape of the head were normal. There was no evidence of prognathism. The body measurements are shown in table 1. The height was 13.5 inches above the average height for his age. The arm span was greater than the height. The distance from the pubic bone to the floor was 13.9 inches longer than the sitting height. The hips were broad and the shoulders narrow. He had bowing of the thighs. The pupils reacted promptly to light and accommodation. The fundi and visual fields were normal. The skin was velvety. There was no beard, practically no hair on the axillae and the pubic hair was scant with a female distribution. There was a pronounced dorso-lumbar kyphosis. The thyroid gland was of normal size. Examination of heart, lungs and abdomen revealed no abnormalities. The penis was of average

size. Both testicles were in the scrotum. The right was of normal size and a little larger than the left one. The lobes of the prostate gland could not be felt. The fingers were very long but not tapering, they were thin throughout their entire length, except for definite thickening of the joints. There was a deformity of the toes of both feet, more prominent on the right foot.<sup>1</sup> Above the right ankle there was an eczematoid dermatitis surrounding a traumatic ulceration. The



Fig. 2. Roentgen photograph of the hand of Raymond (left), aged 19 years, and of a male average size and the same age (right). The photographs were made simultaneously on the same plate.

TABLE 1. MEASUREMENTS OF LAWRENCE D.

Weight	74.3 kg.	163.5 lb.
Height	2128 mm.	83.0 in.
Pubic bone = floor ht.,	1195 mm.	46.6 in.
Span	2080 mm.	81.1 in.
Circumference of		
head	565 mm.	22.0 in.
chest	885 mm.	34.5 in.
abdomen	715 mm.	27.9 in.
Bi-acromial width	355 mm.	13.8 in.
Bi-iliac width	330 mm.	12.9 in.
Left hand length	245 mm.	9.5 in.
Left hand breadth	87 mm.	3.4 in.
Third finger length	110 mm.	4.3 in.
Left foot breadth	108 mm.	4.2 in.
Left foot length	347 mm.	13.5 in.
Great toe length	79 mm.	3.1 in.

TABLE 2. MEASUREMENTS OF RAYMOND D.

Weight	35.5 kg.	78.1 lb.
Height	1586 mm.	61.8 in.
Pubic bone = floor ht.,	835 mm.	32.6 in.
Span	1594 mm.	62.2 in.
Circumference of		
head	527 mm.	20.5 in.
chest	620 mm.	24.2 in.
abdomen	570 mm.	22.2 in.
Bi-acromial width	290 mm.	11.3 in.
Bi-iliac width	225 mm.	8.8 in.
Left hand length	185 mm.	7.2 in.
Left hand breadth	68 mm.	2.6 in.
Third finger length	88 mm.	3.4 in.
Left foot length	281 mm.	10.6 in.
Left foot breadth	82 mm.	3.2 in.
Great toe length	70 mm.	2.7 in.

basal metabolic rate was -7 per cent. The blood Kahn reaction was negative. The blood cholesterol was 139 mg. per cent; phosphorus, 4.1 mg. per cent; calcium, 10.6 mg. per cent. A sugar tolerance test gave the following results in mg. per cent: Fasting, 81; at 0.5 hour, 106; 1 hour, 123; 2 hours, 108; and 3 hours 59. The blood counts were normal. There were no abnormal findings in the urine. Roentgen-ray examination revealed that the skull was symmetrical. The sella turcica was small, shallow and showed some bridging. The sinuses were markedly enlarged. No epiphyseal closure in the bones of the hands and wrists had taken place. There was an extreme kyphosis of the lower dorsal spine, associated with a mild scoliosis, convexity to the right. What were taken to be the bodies of the eighth, ninth and tenth dorsal vertebrae were very poorly defined and appeared to be the site of a destructive process, diagnosed as osteochondritis dissecans juvenilis.

This case seemed to conform exactly to the classic picture of eunuchoid gigantism. We were, therefore astonished, when our patient brought his youngest brother, aged 10, with him to the clinic, to find the same physical

<sup>1</sup> This he said was acquired by wearing too tight shoes. The toes were unusually long, especially the big toes, and pressed together.

characteristics of skeletal growth, but with apparently normal sexual development.

The family history of the brothers furnished the following data: The relatives on the father's side are all more than 6 feet tall. The father is 6 ft. 4 in. in height, the mother is of medium height. There are 5 children. The oldest is described above. The oldest daughter, 18 years old, is 6 feet tall. She shows no signs of endocrine disturbance. A boy of 16 and a girl of 11 years are of average height and are in no way abnormal.

#### CASE REPORT

The patient's brother, *Raymond D.*, age 10 had no complaints. The past history was irrelevant. He started to walk when one year old. He had had measles and diphtheria. An interesting point about his appearance was the striking resemblance to the descriptions of his oldest brother at the age of 10. He, too, was very tall. The height was 9 in. above the average. The span exceeded the height about  $\frac{1}{3}$  in. The distance from the pubic bone to the floor was 3.4 inches longer than the sitting height. He wore shoes of size ten, as did the brother 6 years his senior. The exact measurements are given in table 2. There were no abnormalities of the head and no prognathism. He had long extremities, especially long fingers and toes. Particularly noticeable was extreme enlargement of the big toes. There was symmetrical ankylosis of the metacarpophalangeal joints of both thumbs. The posture was good and there was no deviation of the spine. The pupils reacted promptly to light and accommodation. The thyroid gland was of normal size. Examination of lungs, heart and abdomen showed no abnormalities. The penis and testicles were of normal size corresponding to his age. Both testicles showed normal descensus. Axillary and pubic hair had not developed as yet. The basal metabolic rate was -8 per cent. The blood Kahn reaction was negative. The urine was free from albumin and sugar. Roentgen-ray of the skull showed the sella turcica enlarged and deepened. Neither the dorsum nor the floor had undergone any erosion. The other roentgen studies showed that the ossification centers and epiphyseal lines corresponded to his age. The ankylosis of the thumbs did not affect the bony structure and was apparently a fibrous ankylosis.

#### DISCUSSION

In previous discussions of eunuchoid gigantism it has been assumed that the abnormal growth was dependent upon failure of sex gland development at puberty, and to this concept the first case, *Lawrence D.*, seemed to conform. In the second case, however, the characteristics were well under way at the age of 10. One of two conclusions seems inevitable, either that the influence of hypogonadism upon skeletal growth may exist before puberty without hypogonadism, or that eunuchoid characteristics may be present, occurring perhaps as an hereditary or familial characteristic.

#### SUMMARY

The physical status of patients with eunuchoid gigantism is very characteristic and consists of absence of secondary sex characteristics, hypotrichosis and impotence, combined with overgrowth of long bones and open epiphyses. The history of two brothers, 19 and 10 years old, respectively is given. The case of the older boy conforms exactly to the classic picture of eunuchoid gigantism. The younger brother, aged 10, showed the same physical characteristics of skeletal growth, but with apparently normal sexual development. One of two conclusions seems inevitable, either that the influence of hypogonadism upon skeletal growth may exist before puberty without hypogonadism, or that eunuchoid characteristics may be present, occurring perhaps as an hereditary or familial characteristic.

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# Ectodermal Disorders in Chronic Hypoparathyroidism

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CHANGES in structures of ectodermal origin in chronic hypoparathyroidism have been described repeatedly. In most cases these disorders were noted as incidental findings of secondary importance. The case which is to be reported presented as a striking part of the clinical picture, skin, hair and nail abnormalities. In addition there were other unusual features.

## CASE REPORT

Mrs. M. M., a 50-year old Slovakian woman, was admitted on Dr. C. L. Brown's service on May 18, 1942, complaining of numbness and stiffness of the hands and feet and a recurrent skin disease. She had been in excellent health until 20 years ago, when at the age of 30 she developed difficulty in breathing. Thyroidectomy was advised and done. Following the operation she was relieved of dyspnea, but 5 days later there occurred numbness of the hands and feet accompanied by stiffness in these extremities. These symptoms were relieved by the administration of a calcium salt. On discharge from the hospital she was advised to take one drachm of calcium lactate by mouth 3 times daily. This she did conscientiously, but in spite of the medication she continued to have attacks of tetany as frequently as 4 or 5 times monthly for the next 13 years. In 1935 her family physician advised the use of parathyroid extract by hypodermic at the onset of tetanic symptoms. In the beginning 2 cc. was effective, but as months passed it became necessary to employ increasing doses, and recently as much as 7 cc. has not controlled the tetany.

Several years after thyroidectomy she noted increasing dryness and coarseness of the skin. In January, 1936, she developed a skin eruption involving the chest, lateral aspects of the trunk, the post-auricular areas, and the dorsal surfaces of the forearms. This

was at first vesicular, but soon became dry and crusted, and after 2 months disappeared entirely. During these 2 months the episodes of tetany increased in frequency and severity. Following this she remained practically free of symptoms for 2 years, at the end of which time, in January, 1938, the skin lesions recurred, this time associated with moderate loss of hair and complete shedding of the finger and toe nails. With the reappearance of the skin changes, there was an exacerbation of the tetany. During the next 5 months these symptoms persisted, but at the end of that time, in June, 1938, the skin had again cleared and new nails had appeared. Since then, the dermatologic changes, including loss of hair and nails, have recurred each January and have disappeared each June. For the past 3 years tetany has been rare except during those periods when the ectodermal changes are manifest. Four years ago the vision began to fail, and three years ago a left cataract extraction was done.

The diet has been adequate, including cereals, meats, milk, bread, butter, fresh greens, eggs, vegetables and fruit juices. During the winter months the patient rarely ventures outdoors, but in April and May she sits in the sunlight in the garden several hours each day. In the winter she develops fissures in the angles of the mouth which disappear in the summer.

As a young woman she had had swelling and pain in both ankles lasting a few weeks and leaving no residuum. Six years ago a hysterectomy was performed.

Physical examination revealed a large-boned, moderately obese, middle-aged woman lying comfortably in bed. The hair was partially gray, coarse in texture and sparse in some portions of the scalp. The skin of the arms and legs was dry and coarse. Pigmentation and scaling of the dorsal aspects of both forearms were present. All of the nails showed marked changes, particularly at the lunulae. The lunula of each nail was white and crumbly, while distally the entire nail plate was separated and elevated (fig. 1).

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'The lateral aspects of the trunk presented skin lesions remarkable in appearance—solid purplish-red patches sharply margined from the uninvolved skin (fig. 2). There was thickening of the skin in these patches, and their surfaces were covered with loose flaky scales' (Dr. C. S. Wright). Examination of the eyes by Dr. G. G. Gibson revealed aphakia on the left, the cataract having been removed. An immature cataract was present on the right. This was felt to be of the metabolic type in that there were vacuoles and posterior polar opacities. There were also numerous spicules.

6.8 mg. per cent; serum phosphorus 5.8 mg. per cent; serum protein 6.65 gm. per cent (albumin, 4.76 gm. per cent, globulin 1.89 gm. per cent); serum cholesterol 235 mg. per cent. The Kolmer-Wassermann, Kahn and Kline tests were negative. The Mosenthal test disclosed normal concentration of the urine. Gastric analysis revealed mild hypo-acidity. The B.M.R. was  $\pm 5$  per cent. The electrocardiogram showed a Q interval of 0.40 seconds, the heart rate being 96 per minute, the upper limit of normal for this rate being 0.353 seconds (Ashman and Hull). Because of the



FIG. 1 (left). Nail changes, and Trousseau sign on left in case of chronic hypoparathyroidism.

FIG. 2 (right) Lateral aspect of trunk of patient with chronic hypoparathyroidism demonstrating the extent and severity of the skin lesion (photographed from above).

Examination of the mouth revealed the presence of angular cheilitis, and a smooth reddened tongue with atrophy of the lingual papillae. Upper and lower false dentures were present. There was a thyroidectomy scar, and a small nodule was palpable to the left of the midline which moved on deglutition. The chest was resonant. A few moist râles were audible at the lung bases. The heart sounds were normal, the rhythm regular, the rate 70 per minute, the blood pressure 128/80 mm. Hg. There was evidence of mild left ventricular enlargement. The abdomen was not remarkable. The deep reflexes were active and equal. Chvostek and Trousseau signs were present. It is noteworthy that as soon as the cuff of the sphygmomanometer was inflated there was marked blanching of the skin of the arm.

*Laboratory studies and special examinations.* Blood count: red cells, 3.45 million per cu. mm.; hemoglobin, 9 gm., 57 per cent; color index, 0.87; leucocytes, 8000 per cu. mm.; 52 per cent neutrophils, 36 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophiles. Urinalysis disclosed no abnormal findings except for a very slight trace of albumin. Serum calcium

possibility that the skin and nail changes might have been caused by fungus infection, skin and nail scrapings were examined and cultured. No evidence of fungus was found.

On May 19, therapy was instituted with dihydro tachysterol, 1.25 mg. 3 times daily. This was continued until May 27, the urine being tested 3 times daily with Sulkowitch reagent. (1) A low phosphate diet was ordered, and one drachm of calcium lactate was given 3 times daily by mouth. The patient also received viosterol, 10 minims twice daily in tomato juice, brewer's yeast, one drachm 3 times daily, and daily intramuscular injections of 50 mg. of thiamine chloride and 100 mg. of nicotinamide. On May 27 the Chvostek and Trousseau signs had disappeared, the serum calcium was 7.7 mg. per cent, the serum phosphorus 7.2 mg. per cent, and the Sulkowitch test revealed a faint white cloud. The patient had had no symptoms for one week. By this time the skin lesions had begun to clear remarkably, although it was not unusual for improvement to occur spontaneously at this time of the year. On May 28 the patient insisted on leaving the hospital. She agreed to remain on the

therapeutic plan outlined, except that the dose of dihydrotachysterol was to be regulated by her family physician depending upon the results of the tests with ulkowitz reagent.

The patient was not seen again until Nov. 11, 1942, when she returned as an out-patient for check-up. Several days after she had left the hospital the dose of dihydrotachysterol had been reduced to 1.25 mg. daily, and Sulkowitch tests once a week revealed normal levels of urinary calcium. By June 15, 1942, the skin lesions had disappeared entirely, the nails had red, new nails were appearing, and no further loss of hair had occurred. She had had no tetanic manifestations, and was able to do her housework, had gained 4 lb., and felt better than she had in 20 years. There had been no progression in loss of vision. On examination the pulse rate was 62 per minute, the blood pressure 140/80 mm. Hg. The skin lesions had completely disappeared except for several small light scars. Normal nails were present. The hair was normal in quantity and texture. The scaling on the dorsum of the arms had disappeared. Cheilitis and glossitis were no longer present. The Chvostek and Trousseau signs could not be elicited. There was no blanching of the skin of the arm on inflating the cuff of the sphygmomanometer. The serum calcium was 9.4 mg. per cent; the serum phosphorus 3.4 mg. per cent.

The patient was seen again on March 4, 1943. There had been no recurrence of the ectodermal disorders nor tetany. The serum calcium was 8.9 mg. per cent and the serum phosphorus 1.8 mg. per cent.

#### COMMENT

The unusual aspects of this case are the marked ectodermal changes, the seasonal recurrence, and the evidences of avitaminosis B which disappeared after the institution of treatment.

'Trophic' changes in tetany are not rare. They involve epithelial parts almost exclusively, particularly nails, hair, skin, tooth enamel and ciliary epithelium. At times tetany may be so mild and the symptoms so transient, that the disease may not be diagnosed, yet these changes may occur (2). As early as 1843 Hearard (3) reported changes of the fingernails in tetany.

Other cases presenting loss of the nails have been reported (2,4), although most often the only changes noted are brittleness or grooving with or without necrosis of the nail beds. Schelling felt that these nail disorders were probably the result of angiospasm of the blood vessels nourishing the nail beds. In this regard it is of interest that our patient demonstrated marked blanching of the skin of

the arm below the inflated cuff of a sphygmomanometer.

Coarseness of the hair and loss of hair have been noted (2,4,5,6,7). An acute exacerbation of tetany may be introduced with rapid loss of hair (2). The hair usually returns to normal quantity and texture after the tetany is controlled.

Dryness, roughness, puffiness, thickening and scaling of the skin have been described, (2,4,5,6,7), but we are unaware of the occurrence of pronounced marginated skin lesions similar to those reported here. The dermatologic changes too, have been attributed to angiospasm. Pigmentation of the skin is rare.

Cataract formation in chronic tetany is not uncommon (8). Schelling states that until the advent of modern treatment cataracts were more commonly associated with nutritional tetany in young adults and less frequently in parathyroid tetany (4). The cataracts are characterized by the subcapsular distribution of the opacities (7). The lens may become a gray-white mass. Lenticular changes may occur with surprising rapidity. One patient developed bilateral cataracts to the point of blindness in the space of 4.5 months (7).

Disturbances in tooth formation are commonly seen in chronic hypoparathyroidism (2,4,9,10). Albright states that when hypoparathyroidism develops before the teeth have entirely formed, one finds aplasia or hypoplasia of the teeth from the point in their development that the disease had its onset (9).

Improvement in the ectodermal disorders with improvement in clinical status is not unusual. Haines (11) noted rapid disappearance of the conditions following treatment, and Cantarow (5,6) reported two cases of idiopathic hypoparathyroidism in which hair and skin disorders improved after calcium and parathyroid extract therapy had been instituted.

The seasonal recurrence of ectodermal abnormalities accompanied by an increase in frequency and severity of tetanic seizures during the period from January to May is of interest. Exacerbations during the winter months were noted by Schelling (4). Boothby, Haines, and Pemberton (12) noted that a number of

patients with chronic hypoparathyroidism were much better in the summer and early autumn months than in the winter or early spring. In their experience more cases of parathyroid insufficiency following thyroidectomy occurred in the months of January, February, March, October, November, and December, than occurred in the months of April, May, June, July, August and September. They advised their patients to obtain as much sunlight as possible. Swingle and Rhinhold (13) demonstrated that ultraviolet irradiation caused startling improvement in the violent symptoms following parathyroidectomy in dogs. It is recalled that this patient spent much time in the sunlight in the garden beginning in April or May of each year.

The evidences of vitamin B deficiency, namely the glossitis and angular cheilitis, are difficult to explain inasmuch as the patient consistently took a diet rich in the components of the vitamin B complex. It is of interest that cataracts similar to those occurring in parathyroprivic animals and human beings have been produced in rats by the feeding of a diet deficient in the pellagra-preventing factor (14). Schelling (4) has suggested the possibility that those afflicted with nutritional tetany and cataracts also suffer from deficiency in the P-P factor, or that this factor is utilized but poorly by the tetanic or parathyroprivic organism. In some respects the skin lesions in this case resembled those seen in pellagra, except that their distribution was limited largely to the covered parts of the body. In addition, these lesions cleared when the patient was exposed to sunlight, whereas sunlight is known to aggravate the dermatitis of pellagrins. Against pellagra as the basis for the dermatitis was the

absence of gastro-intestinal symptoms and characteristic neurologic disturbances.

#### SUMMARY

A case of chronic postoperative hypoparathyroidism successfully treated with dihydrotachysterol is presented. The unusual features were the changes involving the skin, nail hair and ciliary epithelium, the remarkable seasonal recurrence of these disorders, and the cheilitis and glossitis which disappeared following therapy.

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# Congenital Myxedema Without Mental Retardation

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IT IS A well-known fact that infantile myxedema, particularly if congenital, is attended by both physical and mental underdevelopment, the latter being characterized by the late appearance or total absence of the successive stages preceding the final mental make-up of the normal child. Such developmental deviation is likely to be accompanied by certain psychic and pathologic disturbances. Mental deficiency, perhaps thyrogenous, in an infant under 10 months of age, is usually betrayed by such signs and symptoms as lack of the sucking reflex, delayed aptitude for holding the head erect, fixing the eyes, recognizing parents and relatives, grasping and playing with objects, turning over, sitting unaided and standing with aid.

Subsequently, the most reliable evidences of mental development will depend on the assimilation of language, walking, control of the sphincters, school progress and mental tests should be added here that results of the latter are by no means absolute, much being contingent on personal interpretation and ruling out of all possible misleading factors. Thyroid insufficiency at these ages is consistently manifested as a reduction of general activity, along with changes in emotional balance, behavior, memory and the power of concentration. These changes are variable in degree and in proportion to the degree of the glandular underfunction, they range from very mild disturbances to definite cretinism. The recognition of the milder forms is of prime interest when the real cause is not overlooked and it is to be borne in mind that these minor psychic disorders are met with in the more subtle hypothyroid states. On the other hand, it is

exceptional that a full-blown and severe infantile myxedema should not present signs and symptoms of mental impairment. While it is true that quite a variety of symptomatic dissociations may be found both in infantile and adult myxedema—as the endocrine insufficiency is apt to attack some systems or organs more than others—we have not encountered in the medical literature so far any single instance of infantile myxedema without marked mental deterioration. For this reason we are reporting the following case.

## CASE REPORT

J C R, male, born in Spain, aged 10 years and 8 months. The chief complaints were underdevelopment, obesity, lack of appetite, constipation, increased thirst and perspiration, sensitiveness to cold, headaches, night terrors, depression, apathy, procrastination and delayed dentition. Growth was about normal until he was 3 years of age at which time there was a slowing which has continued up to the present. The patient weighed 4.5 kg (9.9 lb) at birth and 9 kg (19.8 lb) at 12 months. The weight at present is 15 kg (33 lb) below the minimum normal for the age, but the patient continues to be adipose because of the marked reduction in stature. Notwithstanding this relative obesity, the appetite has gradually decreased. Relatively frequent vomiting occurred during the first months of life while the infant was still breast fed. Constipation, which has become worse for the past few years, is also stated as beginning in early life. Thirst and perspiration, the latter especially during sleep, were found to be rather increased.

The patient complains of sensitivity to cold more intensely felt on the back of the body. Headaches, severe in type, periodic in occurrence and lasting from 24 to 48 hours, began when he was 5 years old. These are not associated with vomiting but are attended by photophobia and conjunctival congestion. The crises of terrors at night began at the age of 5 also.

The patient is an affectionate boy reported as never being cheerful. He is abnormally quiet and is never excited, even after abusive treatment on the part of

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other boys. This is in contrast with the nervous disposition and the propensity to crying which was present up to one and one-half years of age.

Dilatoriness is extreme, but the boy is able to perform a task correctly although slowly. Mental development was normal throughout infancy; holding the head erect, recognition of relatives, walking and talking were normal in the time of their appearance. The sphincters were controlled at the age of 18 months. Apathy began about the third year of life. The intellect is normal at present, if not slightly advanced, according to tests. The patient first became conscious of his shortness in stature about 2 years ago, after other boys made fun of him and called him names; because of this he refused promotion from the third to the fourth grade at school despite being rated as capable.

*Personal history.* He was born at full term, normally delivered and weighed 4.5 kg. (9.9 lb.) at birth. He was breast fed. There was a right inguinal hernia until he was 8 years of age. As already stated, growth was normal until the child was 3 years old. Both deciduous and permanent dentitions were delayed; the mental development has been good. He had no infectious diseases until the age of 7 at which time he had whooping cough without complications. Rhinitis recurs.

*Family history.* The mother of the patient, born in Spain, had her first menstruation at 18. She displays a marked apathy and drowsiness. During the pregnancy she gained about 10 kg. (22 lb.).

*Physical examination.* The patient weighed 25.5 kg. (56.1 lb.; normal for the age, 24–34 kg., 52.8–74.8 lb.). The height was 106 cm. (41.3 in.; normal, 133–142 cm., 51–55 in.), span 105 cm. (40.9 in.); upper measurement, 57 cm. (22.2 in.); lower measurement, 49 cm. (19.1 in.); circumference of the skull, 54 cm. (21 in.); thorax, 60 cm. (23.4 in.); abdomen, 67 cm. (26.1 in.). The height was 27 cm. (10.5 in.) below the minimum normal for the age. The proportion of the body measurements was markedly infantile for the actual age of the patient. The child was plump although the absolute weight was below the minimum normal. The skin was dry, coarse, thick, infiltrated, pale and sallow. There was slight cervical and dorsal lanugal growth. The muscles and bones were somewhat overdeveloped for the small size of the body; the long bones were thick, and the muscles, especially those of the legs were unusually prominent. Lordosis in the lumbar region was conspicuous. The head was relatively large, and the hair dry and thin. There was puffiness of the face; the nose was saddle-shaped. The lips were swollen, the tongue thick and large; there was halitosis. The dentition was markedly delayed; both lower molars, normally appearing at 6, were lacking and only the two upper ones were erupting together with the permanent lower central incisors. The remaining teeth were deciduous. The neck was short and thick, the thyroid was not palpable. There were supraclavicular fat pads. The thorax was thick and adipose. The lungs were normal on auscultation. The heart sounds were normal. The

pulse was 80 per minute; the blood pressure, systolic 90 mm. Hg (it was not possible to determine the diastolic level). The abdomen appeared protuberant, fatty, with tympany. Palpation revealed nothing noteworthy. The genitalia were normal in development for the age. The intelligence quotient, was about 1.13.

*Laboratory findings.* The results of urinalysis were normal; the blood Wassermann reaction, negative; cholesterol, 265 mg. per cent, blood sugar 115 mg per cent; blood count: erythrocytes, 3,650,000; Hb 75 per cent, mean corpuscular volume, 1.02; leukocytes, 8000; neutrophils, 42 per cent; basophils, 1 per cent; monocytes, 1 per cent; lymphocytes, 44 per cent.

Roentgen-ray showed dolichocephaly and the cranial walls to be rather well differentiated, except at the bregma where thinning was present. The sella turcica was enlarged. The sphenoidal and frontal sinuses were lacking. There was a marked osseous retardation of the long bones; the osseous age was 12 years.

*Treatment.* The patient was given thyroid and has been under observation for nearly 2 years. Striking physical improvement was noted at the end of this time. The height increased 16 cm. (6.2 in.). The proportions changed from infantile toward the normal and the child was no longer obese, although the absolute weight showed a gain of 4 kg. (8.8 lb.). Both the osseous and dental ages were greatly influenced by treatment although they are not yet normal. The skin trouble, as well as the sensitivity to cold, constipation and headaches have vanished. The appetite is better. Beneficial results were also obtained in the activity of the patient. He has now passed the fourth grade at school, but there is no improvement in performance. The mental age, as estimated by the mental tests, remains unchanged, *i.e.*, about 12 years. Ruling out the tests to which the boy may get accustomed, and discounting all possible misleading circumstances related to the repetition of such tests, the mental age of the patient is somewhat above 12, the chronologic age being 12 years and 7 months.

#### COMMENT

While the actual presence of an infantile myxedema in this patient is beyond doubt, the question arises as to its inception in this particular instance. Relatively accurate inferences can be drawn in this respect from a careful analysis of the personal history of the case. The absence of the molars normally erupting at the age of 6 affords the surmise that the glandular deficiency set in prior to this age. The severe retardation of the osseous age (4 years), together with the small size of the patient for his age and the diminished activity since the age of 3, lead to the assumption that thyroid underfunction began before the child attained the third year of life. Since no patho-

logic condition apt to impair thyroid function occurred during the first few months following birth, it is probable that the disease is congenital in origin. Practically all thyroid deficiencies are congenital which begin before the age of 5, whatever the time of onset between birth and the fifth year of life. Furthermore, evidence is available, first tooth at 1 year (normal, 6th month), early constipation and overweight at birth (4.5 kg) which points to the patient's having been born with a mild thyroid underfunction which became worse during the first 3 postnatal years and involving chiefly the physical development and affecting only some elements of the mental make-up (emotional activity) while the rest remained normal. The rarity of such a finding in myxedema is the reason for reporting it in a separate paper.

Both psychic and somatic physiologic changes go on uninterruptedly in the young, and the occurrence of a more or less marked

degree of failure of the thyroid gland will undoubtedly have an influence both on growth and on mental development. Again, while symptoms of either physical or mental involvement may predominate in some patients showing a dissociated hypothyroid symptomatology, the instance herein reported is unquestionably an exceptional one in thyroid pathology.

#### SUMMARY

A case of hypothyroidism without mental retardation in a boy, aged 10, is reported.

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# Therapy of Seminal Inadequacy

## I. Use of Pituitary, Chorionic and Equine Gonadotropins<sup>1</sup>

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DURING THE PAST DECADE diverse gonadotropins have been used in the treatment of seminal inadequacy, with varying degrees of success (1-8). Present concepts of male endocrinology, however, lead to expectations of improvement from this therapy only in those patients in whom there is hypogonadotropic pituitary function in conjunction with testes capable of responding to increased gonadotropin levels (9). Therapeutic testing with gonadotropins at present appears to be the only practical clinical expedient for segregating patients likely to be benefited, since no applicable or trustworthy laboratory methods for quantifying pituitary function or testis receptivity are available. This report concerns 21 males with seminal inadequacy whose pretreatment, treatment and posttreatment seminal levels are judged to have been established accurately and whose trials of therapy are regarded as having been well controlled.

### METHODS OF STUDY

The diagnosis of impaired seminal function of the 21 males was made during diagnostic surveys of couples made because of sterile mating of 2 or more years' duration. In addition to seminal studies endocrine and urologic surveys

were made. All the patients had basal metabolic rate determinations and roentgenograms of the sella turcica. Frequently the levels of urinary 17-ketosteroid excretion were established.

Seminal specimens were studied prior to, during and after therapy. Adequate continence preceded the collection of specimens. All seminal fluid was collected directly and without the use of condoms. Examinations were made within 15 minutes to 1 hour after ejaculation.

The usually accepted criteria for seminal normality were employed: *volume*, 4 cc.; *immediate motility*, 80 to 95 per cent; *minimal count*, 60,000,000 per cc. or 240,000,000 for the entire ejaculate; *normal morphology*, 80 to 95 per cent.

More than one pretreatment seminal specimen was examined in all but 5 instances. Total numbers of specimens per patient varied from 17 to 3, the average being 6.

The therapeutic schedules<sup>3</sup> employed included: pituitary, chorionic and equine gon-

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<sup>2</sup> Parke, Davis and Company Research Fellows in Clinical Endocrinology.

<sup>3</sup> The code numbers (used in the figures and table 1) of the endocrine preparations employed in therapy of the patients and our acknowledgments for the generous supply of these agents follow: C-1, chorionic gonadotropin (APL) of Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; E-1, equine gonadotropin (Anteron) by the Schering Corp., Bloomfield, N. J.; E-2, equine gonadotropin (Gonadogen) by the Upjohn Co., Kalamazoo, Mich.; T.P.-1, testosterone propionate (Oreton) by the Schering Corp., Bloomfield, N. J.; T.P.-2, testosterone propionate (Perandren) by the Ciba Pharmaceutical Products, Inc., Summit, N. J.; P-1, pituitary gonadotropin (Gonadotropic factor) by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; and P-2, extract of post-menopausal urine (Gamone) by E. R. Squibb and Sons, New York, N. Y.

dotropins singly; combined therapy with pituitary and chorionic gonadotropins; and combined therapy with equine gonadotropin and testosterone propionate. The usual schedule embraced daily intramuscular injections or 6 weeks with a rest period of corresponding

responses of these patients and additional ones to another gonadotropin preparation (10).

# CLINICAL DATA

The ages of the patients ranged from 27 to 43 years. None of them exhibited signs of

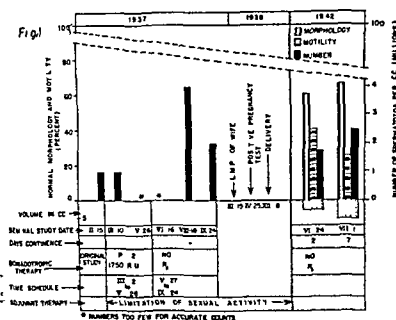


Fig 2

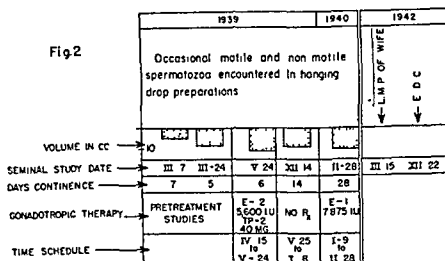


Fig 3

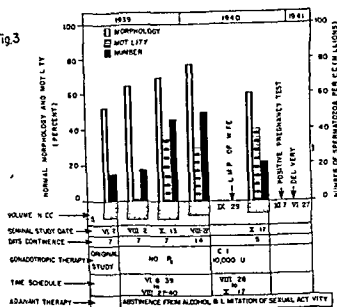


Fig 4

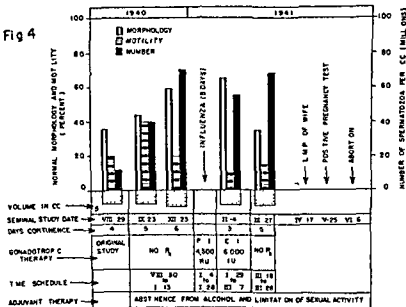


FIG 1. Clinical data on patient described in case 1

FIG 2. Clinical data on patient described in case 3

FIG 3. Clinical data on patient described in case 5

FIG 4. Clinical data on patient described in case 8

duration before additional treatment was given. The majority of patients received more than one type of gonadotropin and more than one series of treatments.

When hypometabolism made advisable the use of thyroid protein or when hygienic errors or constitutional factors existed, seminal alterations incidental to appropriate adjuvant therapy were assessed before the gonadotropic schedules were initiated.

The periods of observation of our patients varied from 3 months to 5½ years. Six of these patients remain under observation and therapy, a subsequent report will deal with the

pituitary or androgenic deficiency. They were classified into 3 groups on the basis of physical findings *Group I*. Those with normal urologic findings except for seminal inadequacy (*cases 1 to 12*); *Group II*. Those with apparent partial atrophy of one or both testes but with no evidence of androgenic deficits (*cases 13 to 16*); *Group III*. Those with chronic epididymitis and chronic prostatitis (*cases 17 to 21*).

The pertinent clinical data on these 21 patients are summarized in table 1. For analytical purposes averaged seminal levels are reported in terms of total motile spermatozoa (T.M.S.=volume of ejaculate in cc.Xim-



mediate motility X number of spermatozoa per cc.) rather than by presenting the four factors of each individual seminal count. These factors for each seminal study of every patient have been plotted graphically and are available for detailed analysis. Figures 1 to 4 give graphically the detailed data for 4 males of *Group I* whose wives became pregnant.

Marked variations characterized values for

the different seminal factors of the individual patient. Since these variations were observed to be apparently of the same magnitude prior to therapy as during therapy, they were taken into account in our attempt to assess therapeutic salvage. Table 2 represents the results of analyses for these variabilities in the case of 12 patients for whom the data were more ample.

TABLE 1. SUMMARY OF CLINICAL DATA OF 21 MALES WITH SEMINAL INADEQUACY

Case Number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pretreatment Values		Total Dosage	Average Treatment Values		Average Delayed Post-Treatment Values		Follow up		
				Number, Sem. Exams.	Total Motile Sperms, Millions		Number, Sem. Exams.	Total Motile Sperms, Millions	Number, Sem. Exams.	Total Motile Sperms, Millions	Wife Became Pregnant	Further Study	
Group I													
1	38	2		1	(Incomplete data: spermatozoa 1,000,000/c.c.)	P-2, 1,750 R.U.	2	(Incomplete data: spermatozoa 1,000,000/c.c. and T.F.C.)	2	(Incomplete data: spermatozoa 3,000,000/c.c.)	Yes (Fig. 1)	Yes	
2	35	3		2	98.5	E-2, 3,600 I.U. E-2, 12,000 I.U.; T.P.-1, 70 mg.	1 33.0 2 100.4		2	41.6	No	No	
3	29	2		2	T.F.C. <sup>1</sup>	E-2, 5,600 I.U. T.P.-2, 40 mg.	1 T.F.C.		1	T.F.C.	Yes (Fig. 2)	No	
4	34	6		1	0.1	E-1, 7,875 I.U. C-1, 18,000 I.U. P-1, 18,000 R.U. C-1, 20,000 I.U.	1 T.F.C. 2 T.F.C.		1	T.F.C.	No	No	
5	42	3½		3	54.8	C-1, 10,000 I.U.	1 (Incomplete data: spermatozoa 2,800,000/c.c.) 32.9		1	7.5	Yes (Fig. 3)	No	
6	42	8		3	276.0 <sup>2</sup>	C-1, 21,000 I.U.	1 217.0 <sup>2</sup>				No	No	
7	39	4		2	T.F.C.	P-1, 14,700 R.U. C-1, 18,000 I.U.	2 T.F.C. 1 T.F.C.		2 1	T.F.C. T.F.C.	No	Yes	
8	34	5		3	47.9	P-1, 4,500 R.U.	1 24.7				Yes (Fig. 4)	No	
9	32	5		3	3.2	C-1, 16,000 I.U.	1 45.4				No	Yes	
10	32	4½		2	309.5 <sup>3</sup>	C-1, 25,500 I.U.	3 5.1		2	5.6	No	No	
11	36	4		2	55.6	C-1, 21,000 I.U.	2 255.0 <sup>3</sup>		2	153.5	No	No	
12	31	2		3	203.6 <sup>4</sup>	C-1, 29,000 I.U. C-1, 10,500 I.U.	2 18.0 1 217.5 <sup>4</sup>		1	148.7	No	Yes	
Group II													
13	30	2	Right testis about ½ normal size. Left somewhat hypertrophied	4	28.6	P-1, 46,000 R.U. C-1, 13,200 I.U. P-1, 13,200 R.U. E-1, 6,750 I.U.	6 53.0		2 2 3	69.0 17.0 19.6	No	Yes	
14	27	2	Moderate atrophy of both testes	1	T.F.C.	E-2, 28,800 I.U. C-1, 16,200 I.U.	2 T.F.C. 2 T.F.C.		1	T.F.C.	No	No	
15	39	6½	Partial atrophy of right testis; orchidopexy 12 years ago	2	0	E-1, 15,750 I.U. C-1, 12,600 I.U.	2 42.0 1 2.2				No	No	
16	42	11	Partial atrophy of both testes	1	aspermia	P-1, 12,600 R.U. C-1, 7,200 I.U. P-1, 30,300 R.U. E-2, 6,000 I.U. T.P.-1, 37.5 mg.	1 0 2 aspermia 1 aspermia		2 1 1	3.5 aspermia aspermia	No	No	

TABLE 1 (Continued)

Case Number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pretreatment Values			Average Treatment Values			Average Delayed Post-Treatment Values		Follow up	
				Number, Sem Exams	Total Motile Sperms, Millions	Total Dosage	Number, Sem Exams	Total Motile Sperms, Millions	Number, Sem Exams	Total Motile Sperms, Millions	Wife Became Pregnant	Further Study and Rx	
Group III													
17	27	5	Chronic prostatitis	3	36 1	P 1, 9,600 R U	1	43 7	2	25 3	No	No	
18	43	15	Chronic prostatitis Right epididymis enlarged and thickened	2	T F C	C 1, 6,600 I U P 1, 6,000 R U	1	aspermia			No	No	
19	39	4	Moderate atrophy of left testis Both epididymides thickened	1	2 8	C 1, 5,400 I U P 1, 2,700 R U E 1, 15,000 I U	1	2 6	1	3 9	No	No	
20	32	7	Moderate induration of prostate and both epididymides	2	T F C	P-1, 5,100 R U	1	aspermia			No	No	
21	30	8	Both epididymides moderately thickened	3	T F C	P 1, 8,700 R U	1	1 5	3	40 3	No	Yes	

## Explanatory Notes

See footnote 3 under Methods of Study for legends of codes of therapy

<sup>1</sup> T F C indicates too few spermatozoa to count

<sup>2</sup> \* indicate instances in which the pathological seminal finding, i.e., decreased percentage of normal morphology, which occasioned therapy is not reflected in the formula T M S (total motile spermatozoa) \* corresponding pretreatment and treatment values for normal morphology in case 6 are 38% and 59%, \* similarly these pretreatment, treatment and post treatment values for case 10 are 66%, 57% and 63%, and <sup>4</sup> for case 12 these are 67%, 45% and 66%

## DISCUSSION

Despite reports by other workers of apparent improvements in seminal values incidental to therapy with various gonadotropins, our data provide no evidence that significant enhancements of seminal function were associated with the treatment schedules employed. In view of the fact that our patients are typically representative of male members of childless couples and may be judged to have been at least partly responsible for the sterile mating of these couples and since the various gonadotropins are employed widely in the therapy of these patients, this report seems justified despite the negative results obtained.

We employed chorionic and equine gonadotropins in doses which were as large as, or larger than, those commonly used and which should have been adequate as judged by their ability to evoke specific ovarian responses in

the female, and likewise definite increases in the androgen secretion of the testes of adolescent males. The doses of pituitary gonadotropin were admittedly inadequate, due to the low potency of available preparations. Therapeutic schedules were as extended as considerations of antibody formation were deemed to permit. Responses to therapy were sampled by seminal studies during the last week of treatment and after 6 weeks of rest from treatment.

Despite the fact that the patients of Group I were thought by their freedom from pertinent urogenital findings to offer the best therapeutic possibilities, only 1 patient (case 2, table 1) experienced slight improvement in seminal values during therapy. Two patients of Group II (case 13 and 15, table 1) and two of Group III (case 17 and 21, table 1) yielded moderately higher seminal values during treatment

TABLE 2. SUMMARY OF PRE-TREATMENT AND TREATMENT DATA OF PATIENTS WITH SEMINAL INADEQUACY

Gonadotropic Therapy <sup>1</sup>	Group <sup>2</sup>	Seminal Factor <sup>3</sup>	I. Average pretreatment values for the indicated groups.	II. Ranges of percentile deviation of average individual pretreatment values from the corresponding ones for the group.	III. Ranges of percentile deviation of single pretreatment values from average individual pretreatment ones.	IV. The percentile deviations of group treatment values from group pre-treatment ones.	V. Ranges of percentile deviation of single treatment values from average individual treatment ones.	
Chorionic	I	V	4.7 c.c.	- 58 to + 36	- 20 to + 32	- 9	- 7 to + 7	
		C	58,000,000/c.c.	- 72 to +116	- 90 to +145	+ 16	- 96 to + 9	
		NM	55%	- 31 to + 22	- 22 to + 29	- 4	- 20 to + 16	
	II	M	37%	- 73 to + 78	-100 to +250	- 6	-100 to +250	
		V	1.5 c.c.		- 33 to + 33	+ 33		
		C	77,500,000/c.c.		- 45 to + 45	+ 28		
Equine	I	NM	50%		- 30 to + 40	+ 42		
		M	3%		-100 to +223	-100		
		V	6.1 c.c.		- 34 to + 31	- 18		
	II	C	20,500,000/c.c.		- 61 to + 45	- 47		
		NM	23%		- 65 to + 52	+ 43		
		M	48%		- 75 to + 46	+ 25		
	III	V	3.5 c.c.	- 7 to +166	- 33 to + 33	+ 75	- 33 to + 33	
		C	33,600,000/c.c.	- 42 to +171	- 86 to +212	+ 46	- 42 to + 42	
		NM	56%	- 10 to + 46	- 60 to + 21	+ 23	- 10 to + 11	
	III	M	40%	-100 to +223	-100 to +223	+ 66	-100 to +100	
		V	3.6 c.c.		- 30 to + 39	+ 3		
		C	2,900,000/c.c.		- 33 to + 45	- 48		
Pituitary	I	M	43%		- 7 to + 16	- 7		
		V	4.3 c.c.		- 7 to + 16	+ 5		
		C	40,500,000/c.c.		- 70 to + 73	+ 36		
	II	NM	46%		- 22 to + 29	+ 41		
		M	37%		- 26 to + 48	- 63		
		V	4.3 c.c.	+ 11 to + 63	- 16 to + 40	+ 35	- 14 to + 21	
	III	C	15,700,000/c.c.	- 81 to +218	- 86 to +212	+ 15	- 83 to +171	
		NM	57%	- 21 to + 3	- 60 to + 21	- 9	- 13 to + 13	
		M	54%	- 72 to + 40	- 81 to + 66	- 2	- 71 to + 43	
	III	V	4.7 c.c.		- 25 to + 28	+ 6		
		C	23,000,000/c.c.		- 59 to +139	- 24		
		NM	41%		- 52 to + 80	- 49		
Chorionic Pituitary	II	M	40%		- 75 to + 50	+ 25		
		V	1.5 c.c.		- 33 to + 33	+ 33		
		C	77,500,000/c.c.		- 45 to + 55	+ 42		
	II	NM	50%		- 30 to + 40	+ 52		
Equine Testosterone Propionate		M	3%		-100 to +223	- 66		
		V	6.1 c.c.		- 34 to + 31	+ 31	0	
I	C	20,500,000/c.c.		- 61 to + 45	+ 13	- 5 to + 32		
	NM	23%		- 65 to + 52	+ 80	- 30 to +130		
	M	48%		- 75 to + 46	+ 4	- 48 to + 56		

<sup>1</sup> *Chorionic Gonadotropin*: Group I, 7 patients, 11 series, averaging 6 weeks in duration with an average total dose of 13,000 I.U.; Group II, 1 patient, 1 series, 4 weeks in duration with a total dose of 7,200 I.U. *Equine Gonadotropin*: Group I, 1 patient, 1 series, 6 weeks in duration with a total dose of 3,600 I.U.; Group II, 2 patients, 3 series, averaging 5 weeks in duration with an average total dose of 7,500 I.U.; Group III, 1 patient, 1 series, 8 weeks in duration, with a total dose of 15,000 I.U. *Pituitary Gonadotropin*: Group I, 1 patient, 1 series, 2 weeks in duration with a total dose of 4,500 R.U.; Group II, 1 patient, 3 series, averaging 8 weeks in duration with an average total dosage of 15,200 R.U.; Group III, 1 patient, 1 series, 6 weeks in duration with a total dose of 9,600 R.U. *Chorionic and Pituitary Gonadotropin*: Group II, 1 patient, 1 series, 6 weeks in duration with a total dose of 12,600 I.U. and 12,600 R.U., respectively. *Equine Gonadotropin and Testosterone Propionate*: Group I, 1 patient, 1 series, 9 weeks in duration with a total dose of 12,000 I.U. and 70 mg., respectively.

<sup>2</sup> Group I, II, III: these are the same as previously defined.

<sup>3</sup> Seminal factors: V, volume; C, number of spermatozoa per cc.; NM, normal morphology; M, motility.

but these values were not sustained when treatments were discontinued. The employment of the total number of motile spermatozoa in an ejaculate as a criterion for evaluating therapy appears justified and practical: the foregoing assessments were on this basis. The inclusion

of data on morphology in a formula for fertility index, *i.e.*, total number of motile spermatozoa of normal morphology, is impossible at present due to the non-availability of suitable supravital stains.

Of the 5 patients whose seminal values i

improved during therapy, three had received pituitary gonadotropin and two equine gonadotropin. Reference to table 2 will substantiate the statement that the apparent improvement of these patients might be related to spontaneous fluctuations in seminal values, since the changes observed during therapy were of no greater magnitude than those observed in some patients during pretreatment studies. In no instance were the treatment alterations in seminal values judged to be great enough to warrant the assumption that the fertility of these patients had been significantly enhanced.

Although the wives of 4 of the 12 males of Group I ultimately became pregnant, reference to figures 1 to 4 will indicate that it is impossible to correlate these pregnancies with any improvements in seminal values incidental to therapy.

Analysis of our data failed to demonstrate that gonadotropic therapy improves any particular factor studied in the seminal examination, either volume, number of spermatozoa, morphology or immediate motility. Furthermore, there was observed to be no correlation between the degree of seminal impairment and the effectiveness of therapy.

Although subsequent experience with purer, more potent and more completely fractionated pituitary extracts which contain the 'follicle-stimulating' gonadotropin may alter our present views, we are inclined to believe that the cause or causes of seminal inadequacy of this group, and of patients in general, are others than hypogonadotropic pituitary failure. A critical study of the effectiveness of the currently available gonadotropins in the treatment of patients whose seminal failure can be related with certainty to undeniable pituitary disease would provide pertinent information. None of the patients treated by us permitted this diagnosis, indeed, very few husbands with pituitary failure are found in couples who seek medical counsel because of sterile mating.

## SUMMARY

Twenty-one male members of childless couples with seminal inadequacy, whose ages (when first seen) ranged from 27 to 43 years and the duration of whose sterile matings ranged from 2 to 15 years, were investigated and treated with various gonadotropins.

Twelve patients presented no signs of endrologic disease, four had partial atrophy of one or both testes; five gave evidence of chronic epididymitis and/or prostatitis. None presented symptoms or signs of pituitary disease or androgenic deficiency.

The following therapeutic schedules were employed: (average series comprised six weeks of daily injections) chorionic gonadotropin, 16 series, average dosage for series 12,600 i.u., pituitary gonadotropin, 11 series, average dosage for series 10,800 R.U., equine gonadotropin, 8 series, average dosage for series 9,700 i.u., and in addition 6 combined series of pituitary and chorionic gonadotropin and 5 combined series of equine gonadotropin and testosterone propionate.

Analysis of treatment data which took into account spontaneous fluctuations of values of various seminal factors, failed to establish any significant enhancement of seminal values relatable to therapy, despite the fact that the wives of 4 patients became pregnant.

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# The Physiology of the Endocrines in Pregnancy, Lactation and the Puerperium

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IT WOULD NOT be possible, within the limits of a short review, to survey with any completeness the enormous literature pertaining to the endocrine aspects of pregnancy, lactation and the puerperium. Nor would this be desirable in a review prepared for a journal the primary purpose of which is to present the clinical aspects of endocrinology, chiefly for the benefit of general practitioners. But clinical endocrinology, if it is to be intelligible, must be based upon what is known of the physiology of the endocrines. This paper, therefore, aims merely to summarize some of the more important physiologic contributions of the past few years which have a rather obvious bearing on the interpretation and management of clinical problems in this particular field. Since there is much overlapping in the endocrine aspects of pregnancy, lactation and the puerperium, there would seem to be no advantage, and some disadvantage in separating one from another for purposes of discussion.

The physiologic problems in which, it seems to me, the general practitioner is most likely to be interested are *a)* the hormone rôle of the corpus luteum and the placenta in pregnancy; *b)* the influence of various hormones upon the motility of the uterine musculature; *c)* the probable rôle of the hormones in the initiation of labor; *d)* the endocrines concerned in mammary development and in lactation; and *e)* menstruation and ovulation during lactation. Many other topics suggest themselves, but those mentioned must suffice for a paper of considerate length. In some of these problems important advances have been made in the

past few years; in others it cannot be said that a great deal has been added to established fact or to previously accepted theories.

*Rôle of corpus luteum and placenta in pregnancy.* The numerous studies of the past few years have apparently established the sequence of the rôle of the corpus luteum of pregnancy and the placental trophoblast in the production of progesterone. Moreover, the work of Brown, Venning and Henry (1, 2) indicates that, on the basis of studies of pregnanediol excretion, the placenta takes over the chief burden of progesterone production from the corpus luteum at a comparatively early stage of pregnancy, from the late second to the third month. On the other hand, Cope (3) has recently called attention to certain limitations in the interpretation of pregnanediol excretion, urging that the output may possibly reflect the state of the endometrium in early pregnancy more than the activity of the corpus luteum. He believes that the pregnanediol excreted probably represents only a small proportion of the endogenous progesterone, although qualitatively it is a good index of corpus luteum activity in either the pregnant or non-pregnant woman. It will be recalled that Hamblen and his co-workers (4) have long stressed the probable rôle of the endometrium in the fate of progesterone, and Cope calls attention to the discrepancy between the relatively large amounts of pregnanediol recovered after progesterone injection by Venning and Browne (1, 2) and the failure to recover any of the excretion product by Hamblen, Ashley and Baptist (4, 5), as well as by Stover and Pratt (6). Cope's own results were intermediate between these extremes, and he suggests that unknown factors other than the

endometrium may be involved. If this applies to injected progesterone, it is probably true also of endogenous progesterone.

That the corpus luteum hormone is essential to the maintenance of early pregnancy in some animals, such as the rabbit and rat, has been well established. Moreover, Allen and Corner (7) showed that even after early ablation of the ovaries in pregnant rabbits the administration of progesterone will permit pregnancy to continue to term. In other animals, including the primates, the rôle of the corpus luteum is now known to be not nearly so important. In monkeys, Hartman (8) has shown that pregnancy may proceed to term after early removal of the corpus luteum, and there have been many reports in which human pregnancy was not disturbed by early removal of the corpus. This is not equivalent to saying that the corpus luteum hormone is of no importance, for such is not the case, and abortion is not infrequently the result of early removal of the yellow body. The indication, however, is that the production of progesterone may be taken over very early in trophoblastic development. The bearing of this question on the treatment of threatened miscarriage and repeated abortion is manifest, but this will be discussed later.

*Influence of hormones on uterine motility.* This subject has provoked innumerable studies during recent years, and the results of these are brought together in the recently published book of Reynolds (9). There is almost general agreement that the spontaneous rhythmic contractility of the uterine musculature is dependent upon the follicular hormone, while progesterone is an inhibitor of this contractility. From this standpoint the myometrium, therefore, exhibits a definite physiologic cycle paralleling the cycle of the endometrium. On the other hand, a number of workers are in disagreement with these views: Kurzrok, Wiesbader, Mulinos and Watson (10), Wilson and Kurzrok (11), Wilson (12) and Moir (13). For example, the group represented by Wilson and Kurzrok assert that even though, as Knaus (14), Robson (15) and Reynolds believe, the uterus of the rabbit remains quiescent in pregnancy under the influence of progesterone, this is not true of the human uterus. These investigators find that during the follicular phase of

the cycle, contractions are of small amplitude and short duration, and during the luteal phase they increase in amplitude and duration, while decreasing in frequency and tonus. During pregnancy, Wilson (12) finds that the human uterus normally contracts in a totally arrhythmic fashion. It should be remembered, however, that during pregnancy another factor becomes operative, that of uterine distention, and Reynolds (9) believes that this has a profound effect upon the contractility of that organ.

This author sharply criticizes the technique employed in the experiments of Kurzrok and his associates, as well as those of Krohn, Lackner and Soskin (16), and his own studies have led him to believe in the correctness of Knaus' belief that progesterone is an inhibitor of uterine motility during pregnancy. It is difficult for the clinician to evaluate these differing viewpoints intelligently for himself, based as they are upon technical laboratory methods. It is fair to state, however, that the evidence and opinion of most investigators points to the probable correctness of the viewpoint of Knaus and Reynolds.

This question is not without importance in clinical practice, as the assumed quieting effect of progesterone upon uterine motility constitutes at least one reason why this substance has achieved wide vogue in the treatment of threatened miscarriage. There are innumerable clinical reports in the literature indicating its value for this purpose, although many of them are uncritical and of little scientific value.

As was pointed out in a recent paper by the present author (17), the difficulty in interpreting results lies in the absence of satisfactory controls. The occurrence of uterine bleeding has been the chief criterion in the assumption of threatened abortion, but the significance of this symptom is quite variable, and in a large proportion of cases miscarriage does not occur even when no hormone therapy of any kind is employed; hence the benefits of progesterone, when its use is resorted to, are difficult to evaluate. This comment is not a criticism of such treatment, which is rational not only from the standpoint of its effect upon the uterine musculature but for other reasons as well, but it is a criticism of the conclusions drawn by many authors as to percentages of success in

the treatment of threatened abortion. This paper is not meant to deal with the therapeutic aspects of the endocrinology of pregnancy, but the above clinical digression will serve to indicate the practical bearing of physiology upon the treatment of certain pregnancy disorders.

Another clinical problem bearing on the possible influence of hormones on musculature concerns the urinary tract. Hundley and his co-workers (18) have presented evidence which they believe indicates that the dilatation of the ureters seen so often in the late stages of pregnancy may be due to the relaxing action of progesterone upon the smooth muscle. On the other hand, Payne and Hodes (19) were not able in their experiments on dogs to produce ureteral changes demonstrable by intravenous pyelography, especially dilatation, by means of injections of estrogen, progesterone or chorionic hormones. The studies of Brack and Langworthy (20) on rats confirm those of Woolsey and Brooks (21) that the increased capacity of the bladder which they had repeatedly noted in pregnant animals is due to decreased tone, and that progesterone is the hormone probably concerned in bringing this about.

*Probable rôle of hormones in initiation of labor.* The bearing of this question of hormonal control of uterine motility upon the problem of the initiation of labor is evident. The determining forces in parturition would seem to be a) removal of certain inhibiting factors or b) the addition of certain positive factors promoting expulsive contractions, or c) both. Of the first group, progesterone would seem to be most important. Of the second group, the follicular hormone and the oxytocic principle of the posterior pituitary have suggested themselves to many workers. Robson (22) had suggested that the cause of parturition was to be sought in the gradually increasing sensitivity of the uterine muscle to the posterior pituitary hormone, as a result of the steadily increasing amount of estrogenic hormone. On the other hand, Heckel and Allen (23) have shown that in the rabbit parturition is delayed by the continued injection of estrogen in the latter part of pregnancy. They find, also, that under these conditions the corpora lutea are maintained and their continued activity is responsible for the delay in parturition. Their experiments lead them to

conclude that labor occurs because of retrogression of the corpora. These authors suggest that the aging process in the placenta which makes it unable to continue the production of estrogen is a possible cause of the decline of estrogen responsible for the waning of corpus luteum activity. It will be recalled that one of the old theories of pre-hormone days attributed the onset of labor to the increasing ischemia resulting from increasing sclerosis of the placental vessels toward the end of gestation.

*Rôle of hormones in mammary development and lactation.* Since the discovery of the lactogenic hormone by Stricker and Grueter (24), in 1929, an enormous amount of investigation has been devoted to the problem of lactation. While it is universally agreed that this hormone plays an essential part in the phenomenon, the exact mechanism is still far from clear. With regard to the growth of the mammary glands during pregnancy, there is general agreement that the ovarian hormones are responsible. Estrogen has been believed to furnish the hormonal stimulus for the proliferative growth of the duct system, and progesterone for the acinar and lobular development of the breast tissue. However, the mechanism is probably not so simple as this. For example, Selye (25) has reported that in rats progesterone alone, if given in sufficiently large doses, can produce complete mammary growth. Furthermore, Gomez and Turner (26) have shown that neither estrogen alone nor estrogen plus progestin will stimulate mammary growth in the hypophysectomized rat, while anterior pituitary material does induce both duct and lobule-alveolar growth in such an animal. They therefore postulate a pituitary-mammogen theory of mammary-gland growth, according to which 'estrogen stimulates an increased secretion by the anterior pituitary of a duct-growth factor, while progestin plus estrogen causes an increased secretion of a lobule-alveolar growth factor by the pituitary' (27).

The chief discussion of recent years has revolved about the question of why lactation does not occur during pregnancy, and what the factors are which initiate it several days after parturition. As Turner and Meites say, four views have been offered by way of explanation: a) the placenta produces a suppressing agent

uring pregnancy which holds lactation in check; *b*) the mechanical distention of the uterus by the fetus and placenta inhibits lactation; *c*) the secretion of progesterone by the corpora lutea suppresses lactation during pregnancy; and *d*) during pregnancy the comparatively large amounts of estrogen present in the blood stream inhibit the lactation process.

Until the past few years the theory which was apparently most favored, and is still held by many, was that suggested in 1936 by Nelson (28), who believed that during pregnancy estrogen inhibited the secretion of lactogen by the pituitary and that it also exerted an inhibiting effect upon the mammary gland. However, Turner and Meites (29), point out that his theory does not explain the occurrence of simultaneous pregnancy and lactation in certain species, nor does it explain the fact that the augmentation of the lactogen content in the pituitary by estrogen injections is experimentally possible in certain species. Their own studies have shown that the lactogen content of the pituitary remains low throughout pregnancy, but increases from 2 to 4-fold following parturition. These findings indicate, they believe, that lactation fails to occur during pregnancy for the reason that the lactogenic hormone is inadequate to support lactation. Some as yet unknown factor is responsible for the increased production of lactogen after parturition.

As evidence to support his theory of lactation, Nelson has shown that large doses of estrogen are apparently capable of inhibiting lactation in guinea pigs, at least for a time. Other authors had reported similar results for other animals: Parkes and Bellerby (30), Robson (22), Reece and Turner (31), Folley and Kon (32). Moreover, many reports have been made by clinicians of inhibition of lactation by the administration of estrogenic preparations, especially stilbestrol, as well as with androgens: Foss and Phillips (33), Kurzrok and O'Connell (34), Clahr (35), Diddle and Keettel (36), Stewart and Pratt (37), and others. On the other hand, Smith and Smith (38) noted no significant effect on lactation following the administration of 4000 R. U. of estrogen for 6 days.

Meites and Turner likewise question the validity of reported observations upon the human female tending to indicate inhibition of lactation by estrogens or androgens, one obvious objection being that the infants were taken from the breasts when such therapy was begun, this in itself furnishing an adequate explanation of cessation of milk production. As further evidence along this line Abarbanel and Goodfriend (39) and later Abarbanel and Klein (40) found that when suckling was permitted to continue, lactation was not prevented by stilbestrol in doses as high as 500 mg. If even larger amounts, as much as 1000 mg., were given in divided doses, beginning soon after parturition, lactation was not prevented, although it might be delayed for from 2 to 6 days after the last dose of stilbestrol. Similar ineffectiveness for even very large amounts of testosterone propionate, methyl testosterone, anhydro-oxyprogesterone and progesterone have likewise been reported by Abarbanel.

The issue which is apparently involved in this aspect of the problem of lactation would seem to be whether large doses of estrogens or androgens can suppress the lactogenic hormone, as had been suggested by Nelson, and further studies on this point have been reported in the above mentioned paper of Meites and Turner (41). The experiments were made with rats. Large dosages (2 mg. daily) of stilbestrol or testosterone to lactating rats for the first 6 days post partum not only did not decrease the lactogen content in the pituitary, but actually increased it, although some reduction in the amount of milk present in the mammary gland was noted. Incidentally, parturient rats which were not suckled for the first week showed 50 per cent less lactogen in the pituitaries than suckled rats, and the mammary glands were practically devoid of milk. This observation, so in accord with every-day obstetrical experience, throws a revealing light upon clinical reports as to the value of stilbestrol in the inhibition of lactation when the babies are simultaneously taken from the breast.

In another paper Meites and Turner (42) attacked the problem of why the lactogen content of the pituitary is relatively low when the estrogen production is at a high level. Their experiments showed that suitable combinations



of progesterone and estrogen 'either entirely prevented or reduced the increase in lactogenic hormone which could be obtained with estrone alone.' They believe that the lactogen content remains as low in the pregnant as in the non-pregnant state because this progesterone-estrone ratio overrides the lactogen-stimulating effects of estrone. In other words, the deficiency of lactogen explains the lactation inadequacy.

In view of the numerous reports now appearing as to the use of estrogen in the inhibition of lactation and, more particularly in the relief of so-called painful engorgement of the breast, there may be some confusion in the minds of practitioners, in view of what has been said above. This confusion is resolved if one remembers that a sharp distinction is to be drawn between painful engorgement of the breast and the onset of lactation. As Abarbanel and Goodfriend (39) remark, 'most of the clinical reports on the effects of estrogens upon lactation in the human have confused painful engorgement with the onset of lactation.' As regards the former of these, clinical reports agree that estrogens and androgens are effective in its relief. Abarbanel and Klein (40), for example, report that stilbestrol in doses of 25 to 40 mg. prevented painful engorgement in 87.3 per cent of 55 non-nursing mothers. In 20 of these some transitory heaviness, usually painless, was noted in 20 cases on the 5th to the 11th postpartum days. They stress the fact that pregnant and puerperal women are extremely tolerant to stilbestrol, large doses of from 250 mg. a day to 1500 mg. a week producing no harmful effects, nor does there appear to be any toxic effect even in eclampsia or fulminating toxemia. Other authors who have reported good results with the estrogenic therapy of painful engorgement are Diddle and Keettel (36), Beilly and Solomon (43) and Stewart and Pratt (37).

While there is still much to be learned as to the factors responsible for the initiation of lactation, there appears to be a much closer approach to general agreement as to those concerned in its continuance. Selye and his co-workers (44) had shown in 1934 that the nervous stimulus of suckling was an important factor in the maintenance of lactation, once it has been begun, and they offered as the prob-

able explanation for the mechanism that the stimulus brings about an increase in the lactogen of the pituitary. The act of suckling does not appear to be essential for the initiation of lactation, its importance being rather in the later maintenance of that function. This at least applies to rabbits, which were used in the recently published study of Meites and Turner (45). In this animal it was found that even in the initiation of lactation, the act of nursing plays some part in that 'maximum lactation and maximum lactogen in the pituitary cannot be obtained without it. Furthermore, in the absence of nursing after parturition, the lactogen content of the pituitary declines rapidly and milk secretion soon ceased. This observation in a lower species conforms with the everyday clinical experience of obstetricians with human lactation.

*Menstruation and ovulation during lactation*  
During the past year there have been several efforts at study of the much neglected question of the effect of lactation upon menstruation and ovulation. The fact that pregnancy not infrequently occurs during the amenorrhea of lactation has generally been rather complacently explained by the statement that ovulation occurs in the absence of menstruation. Such a belief is difficult to reconcile with what we know as to the sequence of ovulation, corpus luteum maturation and later regression, and then menstrual bleeding. It has therefore seemed more likely that the occurrence of pregnancy during lactation amenorrhea indicates merely fertilization of an egg from a first ovulation, and that if the fertilization had not supervened the ovulation would have been followed by menstruation.

Support has been given to this belief by the recently published study of Topkins (46), based on endometrial biopsies during the period of lactation. The study included 145 biopsies from 28 women, at least 4 biopsy specimens being obtained from each woman, including the time span between 6 and 31 weeks post partum.

Of the 145 specimens, 136 (94 per cent) showed an estrogenic endometrium, and 20 of these (15 per cent) showed evidence of hyperplasia. In only 9 specimens (6 per cent) were progestational changes found, and all of these were associated with the onset of the first men-

trual period. The author concludes that 'the endometrium during the period of lactation amenorrhea is similar to that found in amenorrhea caused by other factors, it shows diminished estrogenic stimulation.' He believes that the suppression of the cycle in women with lactation amenorrhea is complete, while in those who menstruate it is incomplete. This latter statement agrees with the findings of Lass, Smelser and Kurzrok (47), published in 1938, and based on the study of biopsies on 47 women through the postpartum period. These women exhibited 194 fairly regular cycles, of which 106 (55 per cent) were anovulatory or sterile in character, while 82 (45 per cent) cycles were ovulatory in character. Finally, reference may be made also to the report of Griffith and McBride (48) in 1939, who in a study of endometrial biopsies in 21 normal lactating women at intervals of from 3 to 24 weeks post partum found that only one woman had ovulated prior to the re establishment of menstruation.

The hormonal mechanism by which the cycle is inhibited during lactation is still a matter of conjecture, as Tophkin discusses in his paper. The immediate factor is undoubtedly a suppression of the pituitary gonadotropin, but whether this is due to the lactogenic hormone or to some as yet unknown internal secretion of the lactating breast cannot be stated.

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# Endocrine Tumors of the Ovary

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WHAT OVARIAN TUMORS may exert definite and profound effects upon the female organism as a whole has long been known. As early as 1905 (a), Pick called attention to a tumor which he called tubular testicular adenoma, associated with masculinization in a young girl. Since that time other tumors of the ovary have been described which manifest hormonal effects such as feminization, masculinization or other changes, and which have proved of the greatest interest not only to the gynecologist but to every physician. The field which has thus been opened is still under intensive investigation, and although considerable advances have been made, much remains to be done. The clarification of the subject is to a great extent due to the studies of Meyer (1918-1932) who was the first to offer a definitive classification of ovarian tumors in which the endocrine effects were stressed. The difficulties heretofore encountered in the recognition and the correct classification of the tumors, it would appear, have been primarily due to the fact that the studies made were almost entirely along morphologic lines. The advent of improved methods for the isolation and titration of the hormones elaborated by the neoplasms has served not only to prove their endocrine nature, but also to allow for their proper classification. It is to be emphasized that hormonal and chemical investigations offer the greatest hope for a better understanding of the entire subject. It is our conviction that as a result of such studies therapy in the future will be modified to a great degree.

In order to understand the origins of the

endocrine neoplasms a consideration of the embryology of the ovary becomes essential.

In the early embryo the celomic epithelium on its mesial aspect anterior to the mesonephros is seen to proliferate giving rise to a structure in which the cells are high and many-layered. This area is the site of the future genital gland, and in the early stage is undifferentiated showing neither masculine nor feminine gonadal characteristics. In the 5.3 to 7 mm. embryo the cells of the surface layer of the future gonad increase rapidly by mitosis, apparently invade the underlying mesenchyme, and form masses of solid cell cords. At this stage the indifferent sex gland consists of a layer of superficial epithelium, the radially arranged cell cords and a connective tissue framework probably derived from the mesenchyme. This structure is known as the epithelial nucleus. Primitive germ cells now make their appearance both in the surface epithelium and the epithelial nucleus. Their origin is obscure and for the purposes of this paper their development need not be discussed. The origin of the cell cords of the epithelial nucleus is still the source of considerable controversy since many authors, notably Fischel (1929, 1930) believe that they arise from a metamorphosis of the embryonal mesenchyme while others (Goodall, 1919) trace their genesis to the surface epithelium. The point of view taken here is important since it bears a direct relationship to the tumors to be discussed. Transformation into the definite sex gland quickly follows the indifferent stage. After the third fetal month a connective tissue growth appears which replaces many of the cells of the epithelial nucleus and a new epithelial nucleus is formed. Part of this structure now projects into the region of the mesovarium forming the rete ovarii which is surrounded by connective tissue radiating into the sex gland in the form of cords known as rete cords. These usually disappear but may persist into adult life. The cell cords of the epithelial nucleus in the male form the tubular system while in the female they become the granulosa and theca interna cells. Sections of the gland undergoing differentiation show masses of 'egg-balls,' stroma, early ova, genitaloid cells, and surface epithelium (fig. 1). In the final stages there is further proliferation of connective tissue with a resulting differentiation into cortex and medulla, and the isola-

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tion of the primordial graafian follicles either as single entities or arranged in groups. It can readily be seen that the complicated processes involved in this growth and development bear a definite relationship to the tumors of the ovary which appear in later life.

The endocrine neoplasms of the ovary may conveniently be divided into 3 groups: tumors producing feminizing effects; tumors producing masculinizing effects; tumors producing other effects.

### *Tumors Producing Feminizing Effects*

These are 2 in number, the granulosa cell tumor, and the theca cell tumor. Although the effects they produce on the female organism are similar, there are certain distinct differences, especially from the point of view of morphology which makes it necessary to discuss them separately.

*Granulosa cell tumor.* This tumor was first described more than 50 years ago, but its true nature was not recognized until recently. It was at first believed to arise from the primordial follicle because it apparently contained ova-like inclusions in carcinomatous tissue. It was therefore called 'adenoma carcinomatosis folliculare,' (Kahlden 1895), 'adenoma folliculare ovarii' and folliculoma until Liepman showed that the inclusions were not ova but cell secretions or degenerated cells. Schmincke (1914) pointed out the similarity between the cell arrangement of the tumor structure and the cell arrangement of the granulosa cells about the graafian follicle, and Meyer (1918) suggested its origin from the primitive forerunner of the granulosa cells found in the adult graafian follicle. It was accordingly named 'granulosa cell tumor' (V. Werdt 1914). The neoplasm probably has its origin from the cells found in the epithelial nucleus in the primitive gonad which have remained in a state of arrested development, but which would have become the granulosa cells of the follicular apparatus had development proceeded normally.

Pathologically, the granulosa cell tumor is usually unilateral, occurring bilaterally in only 10 per cent of cases. It varies in size from a few millimeters in diameter to twice the size of an adult's head. It is encapsulated, its surface is smooth, usually lobulated, and although

solid in consistency may contain cysts. sessile, and if pedunculated may undergo torsion. On section it presents a medullary cellular, yellowish cut surface, with connective tissue bundles traversing the tumor irregularly resulting in a lobular appearance. When cysts are present they contain a fluid which varies from one that is thin and straw-colored to one that is thickly mucinous or gelatinous. Hemorrhage into the tumor or cysts may occur resulting in necrosis. As seen under the microscope 3 types may be distinguished: folliculoid, the cylindroid and the sarcomatous.

The folliculoid type, as the name would imply, resembles the follicle seen in the normal ovary (fig. 2). It is composed of round polygonal cells, closely packed together, showing central vesicular nuclei. Due to the distribution of connective tissue, varying sized compact masses, the cells of which often have mitoses, are formed. In the center of each cell mass a small cavity is seen and this usually contains one or more degenerating cells resulting in a resemblance to an ovum. The radial arrangement of the granulosa cells about the cavity makes the resemblance quite striking.

The cylindroid type is also composed of granulosa cells, but these are usually cuboidal in shape (fig. 3). The cells are divided into columns or cords by fine connective tissue strands and within the cord spaces a cellular or connective tissue debris can be seen. The arrangement may be quite irregular so as to give a bizarre appearance; cell cords, connective tissue and cystic spaces intermingled freely. The connective tissue may become hyalinized.

The sarcomatous type of granulosa cell tumor is composed of plump, closely packed spindle cells resembling a highly cellular sarcoma. There are large areas of connective tissue and this results in a sarcomatous appearance. However, within the meshes of the connective tissue, collections of granulosa cells can usually be distinguished.

In all 3 types cyst formation may occur due to degeneration of the cells with secretion of fluid which may reach considerable quantities. The epithelial lining of these cysts, when present, is usually low cuboidal in type. Although the cyst fluid may contain the estrogenic hor-

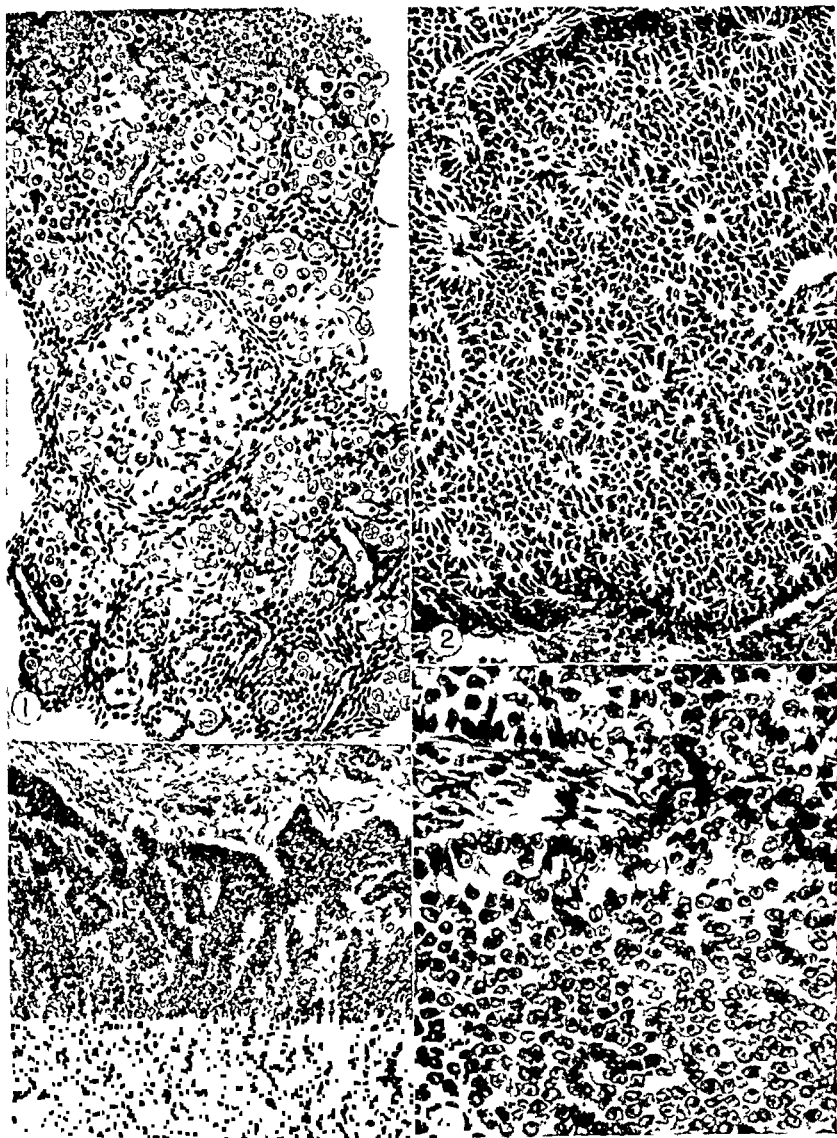


FIG 1 Medium power Differentiated gland with parenchyma showing 'egg balls,' stroma, ova, genitaloid cells, and surface epithelium (From Lubarsch In Halban and Seitz *Biologie und Pathologie des Weibes* Berlin, Urban 1929)

FIG 2 Low power Folliculoid granulosa cell tumor

FIG 3 Low power Cylindromatous granulosa cell tumor

FIG 4 High power Malignant granulosa cell tumor with rosette formation and mitoses.

hormone has already been reported (Geist and Spielman 1935). The extract of the equivalent of 0.75 gm. of tumor tissue was found to contain 1 mouse unit of estrogen. This is more than can be demonstrated in an equivalent quantity of placental tissue and should leave no room for skepticism. Undoubtedly reports of the occurrence of the tumor in children will appear in the future which will further serve to prove its effects. The morphologic, the clinical, the chemical, and the hormonal characteristics are distinctive enough to allow for its classification as a definite entity. The importance of hormonal studies in the individual as well as of the tumor tissue is again stressed.

Treatment of the condition is exactly the same as that described in the discussion of the granulosa cell tumor, *i.e.*, conservatism in the young and hysterectomy with bilateral salpingo-oophorectomy in the senium.

#### TUMORS PRODUCING MASCULINIZING EFFECTS

The tumors of the ovary which produce masculine effects in the individual are extremely interesting. The physical changes in the female harboring such a tumor are so profound that once observed they are never forgotten. However, it must be pointed out here that conditions other than ovarian neoplasms may also produce these changes, and that indiscriminate laparotomies for exploration of the ovaries in the presence of normal palpatory pelvic findings is to be condemned. Thorough investigations to determine the presence, especially, of adrenal cortical tumors or pituitary tumors (basophilic adenoma) in the absence of positive pelvic findings, as well as hormonal blood and urine studies, basal metabolism, blood counts, and vaginal smears, all should be performed before resorting to pelvic surgery. It is not unlikely that many needless operations are being performed in individuals showing some of the stigmata of masculinization, in the hope that a masculinizing tumor will be found. One repeatedly observes cases showing a greater or less degree of hirsutism accompanied by a pelvic tumor which on laparotomy turns out to be a pedunculated fibroid or a simple ovarian cyst which could not by any stretch of the imagination be associated with the virilism manifested by the

patient. It must also be borne in mind that in spite of careful investigation by every means at our disposal no cause whatever may be found for the presence of virilism in many cases.

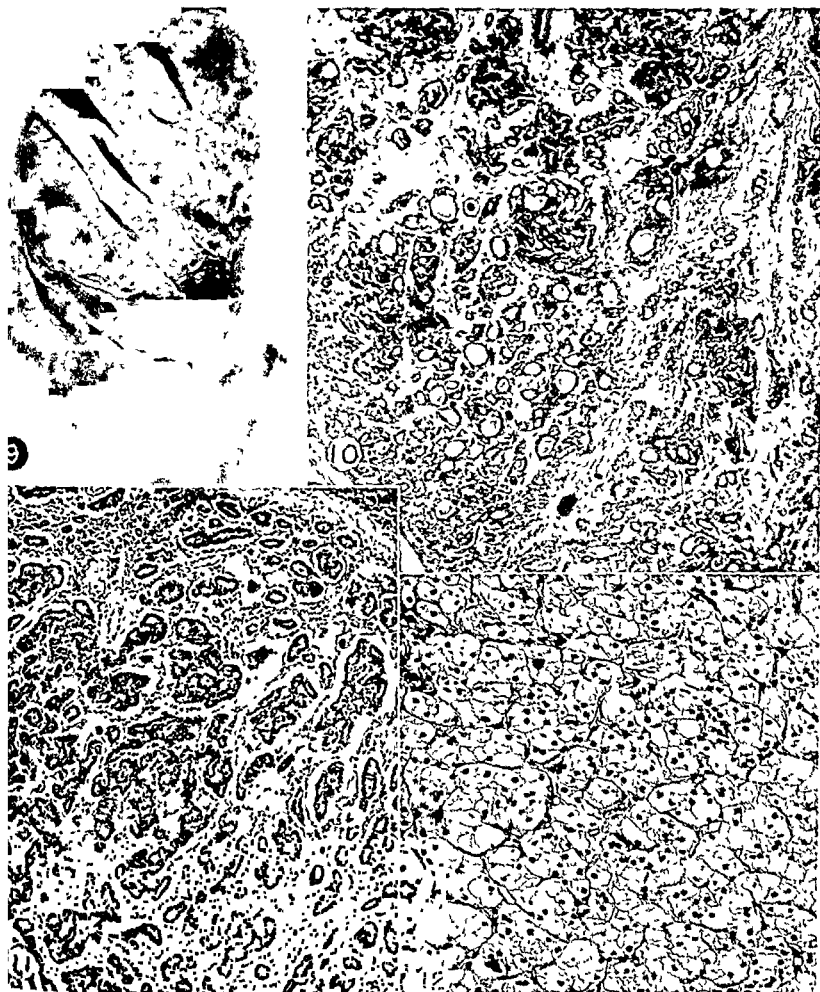
The tumors of the ovary which produce masculinizing effects and which are to be discussed in this paper are: arrhenoblastoma, adrenocortical tumor, 'luteoma,' (solid tumors with luteinization; lutein cell tumor).

*Arrhenoblastoma.* Although Pick (1905) was the first to describe the tumor which we now call the arrhenoblastoma, he believed that it arose from the male portion of a true ovotestis. It remained for Meyer (1930 a) however, properly to classify it by careful morphologic and genetic studies. The overwhelming majority of present day observers believe as he does, that the tumor arises from a male-rected element in the ovary, probably in the rete ovarii and medullary tubules described above, which represent the homologue of the tubuli seminiferi in the male, and which by their persistence give rise to the arrhenoblastoma. About 50 cases have been reported to date.

From the cases already described the variations in size of the tumor are not marked; it usually varies from that of a walnut to the size of a large orange. The surface of the neoplasm is smooth, lobulated, firm and encapsulated. Cystic areas may be present. On section it is seen to be firm in consistency, yellowish gray in color, and scattered areas of hemorrhage and necrosis can be distinguished (fig. 9). There is a tendency towards lobulation, the lobules being well demarcated by the distribution of connective tissue. The yellow areas are also surrounded by connective tissue. Cysts if present are variable in size and contain a clear straw-colored fluid or a turbid dark secretion depending upon the extent of necrosis.

Histologically, Meyer (1930 a) has divided the arrhenoblastoma into 3 types. These are the typical, the atypical, and the intermediate varieties.

The typical form is composed of single layers of low columnar or cuboidal cells which form typical tubular or adenomatous structures (fig. 10). The gland-like arrangement may



g. 9 Section of arrhenoblastoma with cavitation and hemorrhage

g. 10 Low power Intermediate type of arrhenoblastoma with atypical and typical structures Note regularity of some tubules

g. 11 Low power. A typical type of arrhenoblastoma with imperfect tubular arrangement (Courtesy of Dr R Miller)

g. 12 High power. Adrenal rest tumor. (Courtesy of Dr Klein)

semble the interstitial cells of the testicle. The cells show a granular or vacuolated cytoplasm and the nuclei are round or irregular in shape. The tubules are surrounded by connective tissue which contains either a few

spindle cells or many large pale granular cells resembling the so-called interstitial cells of Leydig. They contain lipoid which may be related to the production of hormones. Evidence of malignancy may be present as char-



acterized by mitoses, variations in cell structure, and irregular cell arrangement with a tendency toward invasion of the connective tissue.

The atypical form comprises groups of cells which appear in the main, as solid cords with only an occasional irregularly tortuous tubule (fig. 11). The latter may be convoluted so that no lumen is discernible. The cells are fairly large, oval in shape or spindle-shaped. There is a marked resemblance to sarcoma in some areas. Connective tissue is present between the cord-like structures but this is not as well preserved as in the typical form. There is a greater tendency towards vacuolization of the cells, fatty degeneration, hemorrhage, liquefaction and cyst formation.

The intermediate type presents combinations of the typical and atypical. Both well-formed glandular structures and irregular cell cords can be distinguished.

Although the tumor usually occurs in individuals between the ages of 16 and 50, cases have been reported in the postmenopausal period. The striking and characteristic feature of the arrhenoblastoma is the associated masculinization (or defeminization). In most of the cases reported the degree of masculinization seems to bear a distinct relationship to the degree of differentiation of the cells and their arrangement in the form of tubules, *i.e.*, the closer the approach to the typical form of arrhenoblastoma the fewer the signs of masculinization, and the greater the resemblance to the atypical form, the greater the degree of masculinization. The symptoms and signs consist of amenorrhea; hypertrichosis which is generalized and usually accompanied by a sufficient growth of the beard as to necessitate shaving; hypertension; a loss of the feminine skin texture and general feminine body contour; a deepening of the voice which changes to a baritone in quality; atrophy of the breasts; enlargement of the clitoris; and skeletal changes resulting in a resemblance to the male type. Sterility also occurs even though children may have been borne prior to the development of the tumor. Usually there is a loss of normal libido, accompanied by a variety of psychic disturbances which depend upon the physical changes primarily.

After the removal of the neoplasm the signs and symptoms usually regress almost completely. Changes in the bony structures, as those of the larynx usually persist, however, that the voice may remain deep in quality. Instances of pregnancy with the birth of normal children after the regression of symptoms have been reported.

The association of masculinization with arrhenoblastoma has been explained on the basis of production of large quantities of androgenic hormone on the part of the tumor. Up to this time, probably due to the paucity of material examined, this point has not been proved. As more cases are discovered and intensively studied, especially on a hormonal basis, this problem undoubtedly will be solved.

Treatment consists in extirpation of the growth. Although it is classified as being malignant, its potential of malignancy is not great so that in young women both ovaries need not be removed. However, if the second ovary shows involvement or the patient is in or near the menopause both uterus and adnexa should be extirpated.

*Adrenal rest tumor.* That masculinization may occur in females showing cortical tumor of the adrenal gland is a well established fact. The recognition of the condition and removal of the involved gland has repeatedly resulted in a regression of symptoms. In the ovary this type of tumor may also be encountered and may also produce masculinizing effects. Genetically, it must be remembered that the primitive sex gland develops in close approximation to the mesonephros so that misplaced adrenal cells may come to rest in the region of the ovary as the latter descends into the pelvis. Such masses of lipoid-containing, large, vacuolated cells have been described as being present along the border of the infundibulo-pelvic ligament, within the broad ligament, in the region of the ovarian vessels and within the ovary itself. It seems more than likely that these cells may give rise to neoplasms. Of concern here, of course, is with the primary tumors of this type arising in the ovary. Those associated with tumors of the adrenal gland may be primary and independent in themselves or they may be metastatic. Since adrenal rest growths of the ovary may appear

g after (as much as 20 years) the removal of primary adrenal neoplasm their origin from misplaced cells seems logical.

The tumor varies in size from that of a walnut to a mass as large as a man's head. It is encapsulated, its surface is smooth and nodular, on section its color is yellow or brown. It is soft and elastic in consistency. Connective tissue trabeculae are not conspicuous, usually due to a tendency toward hemorrhage and necrosis. Cystic areas may be present. Although tumors may be confined to the ovary proper in most instances they arise in the broad ligament and spread to the ovary. Microscopically, the growth is composed of large transient vacuolated cells with definite cell membranes (fig. 12). The nuclei are small, stain darkly, and are centrally and eccentrically located. The cells show a mosaic arrangement, found mainly about the numerous fine vesicles, and since there is little connective tissue, they lie directly on the capillary walls. They form rows or tubules.

Clinically, the tumor is usually associated with virilism, although the degree may vary. Some of the symptoms of masculinization described above may be present or only hyperandrogenism and amenorrhea. However, regression of these symptoms upon removal of the neoplasm has repeatedly been seen. It must be emphasized that the adrenal rest tumor is highly malignant and its metastases may be widespread. Also, that the removal of such a tumor does not necessarily mean the eradication of all cells capable of producing the growth. All tumors elsewhere in the pelvis and not recognized may explain the continuation of symptoms even after operation. The fact that the adrenal gland may be involved must also be considered.

It is particularly interesting to note that in adrenal cortical tumors associated with marked masculinization, tremendous quantities of estrogens are produced. The significance of these findings is not at all clear. Studies to determine androgen production by the individual and on the part of the tumor help considerably.

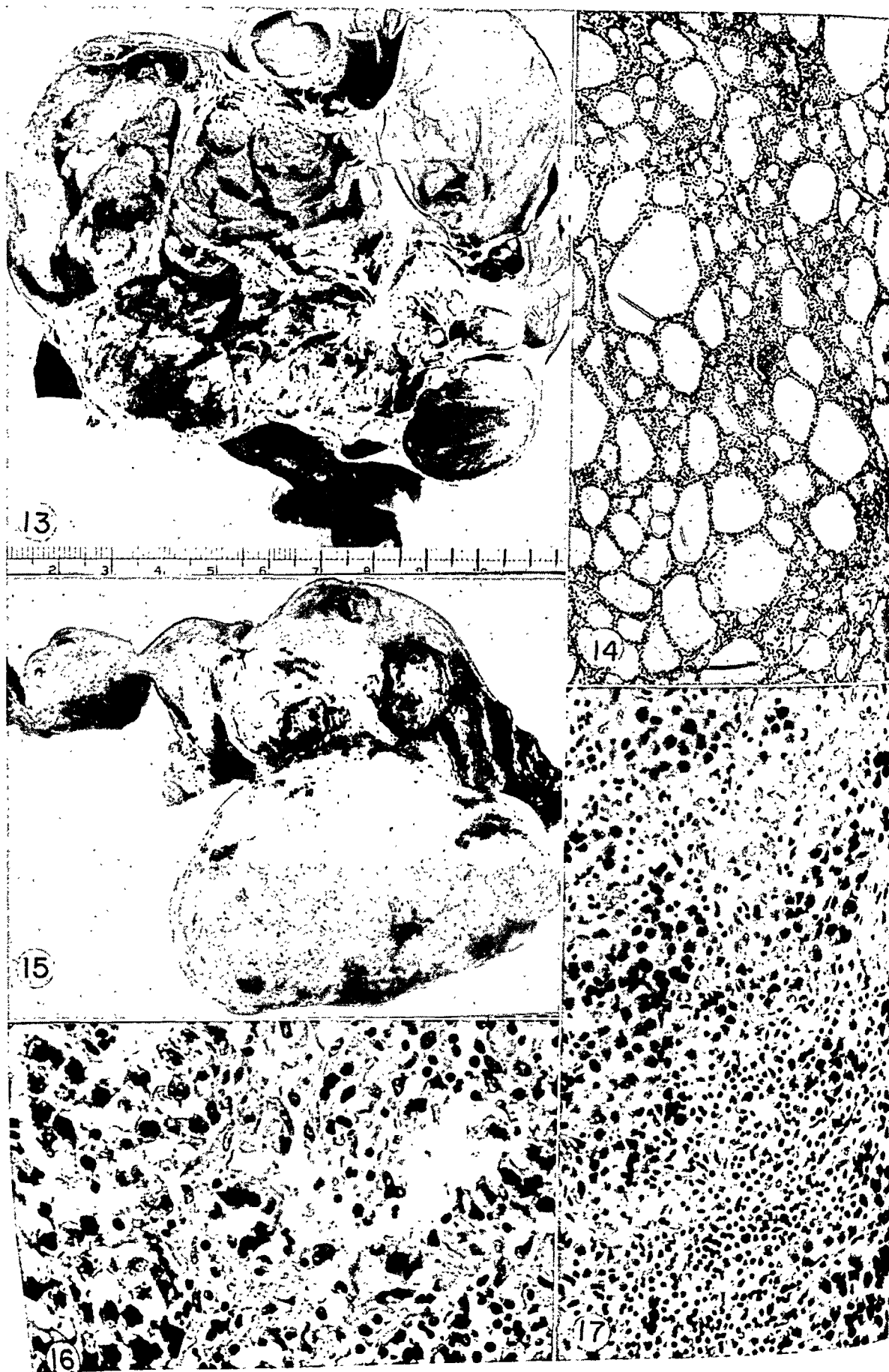
The adrenal rest tumor at present is the cause of much speculation. It is being confused with

luteinized tumors (usually granulosa or theca cell), with the so-called 'luteoma,' and even with atypical Krukenberg tumors. The luteoma is described below. The Krukenberg tumor has never been found to be associated with masculinizing changes, and is, of course, a metastatic tumor from the gastro-intestinal tract.

Treatment consists in operative removal of the neoplasm, if it is primary. Since it is highly malignant, in the young individual careful exploration of the entire pelvis even to splitting the second ovary, if in doubt, should be performed. When the ovarian growth is metastatic from a primary one in the adrenal gland, its removal is only indicated after the affected adrenal has been removed. Radio-therapy post-operatively has been recommended in malignant cases.

'*Luteoma*'; *luteinized tumors*; *lutein cell tumor*. As has been indicated above, the so-called luteoma is the source of controversy at the present time. Only 6 cases have been reported heretofore, and these have by no means proved acceptable as a distinct tumor entity. Because of the similarity of the pathologic picture of adrenal rest tumor, luteoma, and luteinization of other tumors of the ovary these 3 conditions must be carefully evaluated before any conclusion can be reached as to correct diagnosis. The confusion that exists is mainly due to the fact that morphologic studies show that there is little difference between even a mature corpus luteum and adrenal tissue undergoing proliferation within the ovary. Luteinized small granulosa and theca cell tumors may also produce a similar picture. However, differentiation is possible.

The luteoma, from such cases as have been described, appears to cause enlargement of the ovaries which may reach twice normal in size. Its color is yellow and consistency elastic. On section it presents a yellow, moist, glistening surface occasionally containing tiny cystic areas. White connective tissue strands radiate throughout the yellow tissue. Hemorrhage and necrosis are not common. The microscopic picture is exactly the same as that which characterizes the adrenal rest tumor. Lipoid can be demonstrated in the cells but glycogen is absent. The luteoma may also resemble a Krukenberg tumor.



FIGS. 13-17. See opposite page for legend.

Clinically, these tumors should produce a continuous secretory phase type of uterine endometrium. It is true that the premenstrual decidual reaction has repeatedly been described, but it must be emphasized that these changes may also be brought about by luteinized tumors. The masculinization which has also been reported (hypertrichosis, amenorrhea and voice changes), appears to us to be associated with an adrenal rest tumor. In other words, we believe that an ovarian neoplasm which presents the picture of a so-called luteoma, when accompanied by excessive bleeding, enlargement of breasts, and other feminizing influences, probably is a luteinized granulosa or theca cell tumor. On the other hand, when the neoplasm is accompanied by signs of masculinization it is to be regarded as an adrenal rest tumor. Since the evidence of the actual existence of the luteoma is still lacking it would perhaps be better to await further investigations before accepting it as a true ovarian neoplasm.

Luteinization of theca interna cells has been observed in human ovaries and has artificially been produced in rats. Although evidences of masculinization accompanied these findings, the changes are attributable to hormonal effects produced by gonadotropic or adrenal hormones rather than to the luteinization itself.

Treatment, in view of the foregoing, consists in removal of tumor tissue. When bilateral enlargement of the ovaries is the result of hormonal stimulation, operation is not required.

#### *Tumors Producing Effects Other Than Feminization or Masculinization*

In this group 3 types of neoplasm are to be discussed and a fourth merely mentioned. They are: a), struma ovarii; b), dysgerminoma; c), teratoma; and d), the endometrial tumor.

**Struma ovarii.** Struma ovarii is included in the discussion of endocrine tumors of the ovary because it also may produce hormonal effects. It bears no relationship to either feminization or masculinization. Its inclusion is based on the

fact that it is a tumor composed mainly of thyroid tissue which not infrequently produces an excess of the thyroid hormone capable of reacting in the same way as enlargement of the thyroid gland itself.

Although the origin of the tumor may still be debated most observers are agreed that it arises as part of a teratoma in which all or most of the teratomatous elements have been replaced by thyroid tissue. Since small quantities of this tissue are frequently found in teratomas of the ovary, only those cases in which the thyroid element is the only tissue, or predominates in the neoplasm, are to be classified as true struma. About 50 cases have been reported.

Pathologically, the tumor may appear as a tiny nodule or it may be as large as an adult's head (fig. 13). It is encapsulated and its surface is irregularly nodular. On section its color is that of the thyroid gland, waxy and brownish in appearance, and on cut surface it presents a honeycomb-like appearance, the varying-sized spaces being filled with tenacious, yellow-brown secretion. When seen under the microscope, the tissue is composed of alveoli lined by flat or cuboidal epithelial cells which have poorly defined boundaries and which contain small darkly-staining nuclei (fig. 14). In areas the structure may consist only of solid cords of cells in which lumina are absent. Occasionally papillary projections covered by high columnar epithelium are discernible suggesting the hyperplasia of the thyroid gland seen in true hyperthyroidism. There may also be evidence of invasive growth with perforation of the capsule, and this would represent malignancy. Connective tissue is usually scanty. The secretion in the alveoli stains homogeneously and gives the same microchemical reactions as the colloid material of normal thyroid tissue. In this connection many investigators have demonstrated iodine in quantities comparable to those found in the gland itself. Plaut 1933, by biologic tests on tadpoles as well as the Reid-Hunt reaction, identified the teratomatous struma as being true thyroid tissue.

Fig. 13. Struma ovarii. (Courtesy of Dr. Ludwig Emge.)  
Fig. 14. Low power. Struma ovarii. (Courtesy of Dr. Ludwig Emge.)

Fig. 15. Dysgerminoma.

Fig. 16. Teratoma.

Fig. 17. Endometrial tumor.

noma.

From the clinical point of view the most striking symptoms produced by the action of the tumor are those of hyperthyroidism. The loss of weight, tremors, tachycardia, nervousness and elevated basal metabolism correspond to the picture presented in primary involvement of the thyroid gland. The neoplasm may be benign or malignant, and when malignant is invariably accompanied by ascites. Intra-abdominal metastases may also occur.

Treatment consists in operative removal of the neoplasm. In malignant cases hysterectomy with removal of both adnexa should be performed.

*Dysgerminoma.* The dysgerminoma of the ovary is another interesting tumor whose genesis and effect upon the individual is not entirely clear. It is discussed in this paper because reports of its association with one of the hormones (the gonadotropic) have appeared, and because in the general classification of ovarian neoplasms it is related to such tumors as the granulosa cell, theca cell, and arrhenoblastoma (Geist 1942).

As has been described the granulosa and theca cell tumors have their origin in a cell which may be said to be of the feminine type (the granulosa and theca cell), and the arrhenoblastoma in a male-directed cell type. The dysgerminoma, in the opinion of present-day investigators, probably originates from a neuter cell which goes back to the early epithelial nucleus, and which is neither masculine nor feminine from its inception. Absolute proof of this theory is lacking but certain facts seem to support the concept. These include the frequent occurrence of the tumor in underdeveloped or otherwise defective gonads in both males and females, or even in the ovotestis of hermaphrodites. It is also seen in such combinations as an aplastic gonad on one side and a tumor (dysgerminoma) on the other, and ovotestis on one side and tumor on the other. In the male it is called 'seminoma,' and it is also known as large round cell sarcoma.

The neoplasm is rounded, nodular, solid, and surrounded by a thin capsule which may be perforated by the tumor tissue. It may reach the size of an adult's head (fig. 15). On section it is yellowish gray in color, soft and elastic in consistency, and shows a tendency toward hem-

orrhage and necrosis. Cysts are usually present which are the result of degeneration and may vary in size up to that of an orange. The tissue is extremely friable and is easily torn on manipulation. The capsule may be perforated by tumor so as to form adhesions and metastases to surrounding organs. Microscopically, it is found to be composed of large, round or polygonal uniform cells containing granular pale staining cytoplasm and central nuclei which stain darkly. The arrangement of the cells may be in the form of strands, rows, or alveoli, and these are separated from each other by fine connective tissue septa. Giant cells are not infrequently seen often surrounded by fibroblasts resembling granulation tissue (fig. 16). Connective tissue is rather scanty, and it may be hyalinized. One of the striking characteristics of the morphology of the tumor is the lymphocytic infiltration of the connective tissue (fig. 17). Ovarian tissue may be present and show an entirely normal picture with follicles, corpus lutea and stroma.

Clinically, the tumor is usually unilateral but bilateral occurrence is not uncommon. It is found most often in young women either just before or after the onset of puberty, and especially in the hypoplastic, asthenic type. Older normal women, however, may also harbor the neoplasm. The menstrual cycle is usually affected by the presence of the tumor, amenorrhea being the rule. Due to the aplasia or hypoplasia present, there may be no history of the establishment of menstruation. On the other hand, the females may have been entirely normal and may even have borne children. Very few cases have shown menorrhagia or metrorrhagia. Not infrequently one also finds a small atrophic uterus, infantile external genitalia and an enlarged clitoris. Hypertrichosis has rarely been observed. The tumor is highly malignant with metastases and recurrences following operation being common.

It is interesting to note that such hormonal studies as have been performed in individuals manifesting this type of neoplasm, have invariably shown the isolation of a gonadotropic hormone. Thus, Spielman and Morton (1933), Fauvet (1936), and Bluemel (1934) have demonstrated this hormone in the urine or tumor tissue, of both males and females. The reaction

ome of the cases has been strong enough as produce luteinization of the immature anilovary, while the estrogen reaction was negative. Although these findings cannot be examined at the present time, the similarity to the monal conditions which exist at the menopause (increase in gonadotropic, decrease in estrogenic hormones) is suggested. However, additional studies must be made on many more cases before any conclusions are warranted.

The treatment is operative. In older women

tium. Actually, in the authors' opinion, true chorionepithelioma is either secondary or metastatic. It is secondary when it arises following a primary ovarian pregnancy or from the endodermal components of a teratoma, and metastatic when it is the result of metastases from a primary chorionepithelioma elsewhere. It is a true endocrine tumor since it produces tremendous quantities of one of the important hormones, *i.e.* the gonadotropic.

The neoplasm may be very small or may be as large as an adult's head. Its surface is nodular

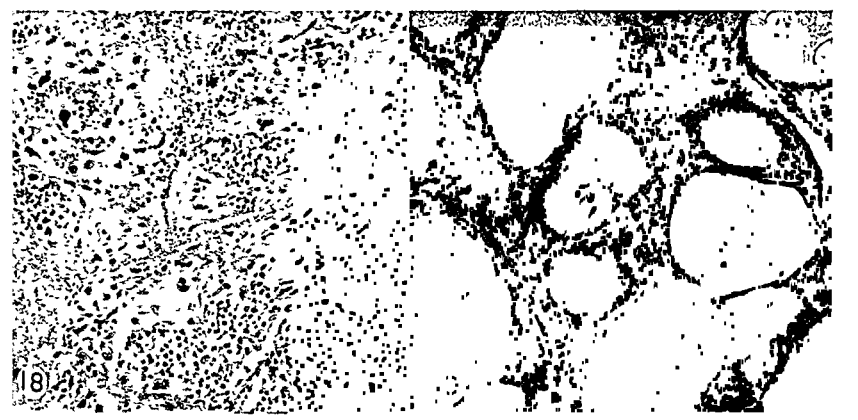


FIG. 18. Low power. Chorionepithelioma of ovary.  
FIG. 19. Medium power. Cell nests composing Brenner tumor with tubules, beginning cyst formation, and pseudomucinous epithelium (lower right).

ical removal of uterus and adnexa is indicated, and in the young, extirpation of all tumor tissue. It is particularly stressed that the second ovary must be carefully investigated for involvement. In one of the cases observed (Spielman and Morton 1938) although one ovary was the site of a large tumor, the other ovary contained only a small nodule about 1 cm. in diameter which could easily have been overlooked. When both ovaries are removed, postoperative radiotherapy should be utilized.

**Chorionepithelioma.** Chorionepithelioma of the ovary is a very rare tumor, and its recognition is usually not easy. Although cases of so-called 'primary' chorionepithelioma have been described, these probably represent either sarcoma or carcinoma in which there is an atypical cell arrangement closely resembling syncy-

and hemorrhagic, and it is usually surrounded by a thin friable capsule. On section it is seen to be reddish-purple in color due to the blood present, and such tissue as can be distinguished resembles placental tissue. The tumor is traversed by firm white translucent bundles and plaques. Microscopically, sections show masses of small, dark-staining nuclei arranged in plaques or rows within an amorphous matrix-like tissue. Cell boundaries are indistinct or may be totally absent, so that the neoplastic tissue appears as large masses of cytoplasm containing numerous nuclei, or large groups of nuclei in relatively little cytoplasm (fig. 18). Associated with this syncytial tissue there may also be collections of relatively large polyhedral cells with distinct cell bodies, granular or vacuolated cytoplasm, and central well-defined

nuclei rich in chromatin. These represent the typical Langhans cells which with syncytium characterize chorionepithelioma. When the tumor has its origin in a teratoma, other types of tissue such as undifferentiated glands, neuroepithelium and cartilage may also be found.

Chorionepithelioma of teratomatous origin is usually found in children and is not infrequently associated with the symptoms of premature puberty already enumerated. The changes in secondary sex characteristics in these cases is due, of course, to the elaboration of the gonadotropic and the estrogenic hormones which act upon the breasts, uterus and vagina to bring about a premature sexual maturity. Neoplasms originating either in primary ovarian pregnancy or from chorionepithelioma elsewhere (metastases) may produce such effects as abnormal uterine bleeding even to the point of severe anemia, enlargement of the breasts, and hyperemia of the vulva and vagina. Regardless of origin it must be recognized that chorionepithelioma is an extremely malignant tumor often accompanied by ascites, pain and weakness, and showing a marked tendency toward early metastases especially to the lungs, the brain and the liver.

As can be seen, hormonal assays of blood and urine will readily differentiate this type of neoplasm from any of the others, since only in hydatid mole or chorionepithelioma of the uterus can such high titers of gonadotropic hormone be demonstrated. An increase in the estrogenic hormone titer is also to be expected.

Although the prognosis is poor, attempts at the radical removal of all neoplastic tissue is always justifiable. Radiotherapy alone has been advocated by some observers due to the danger of dissemination of tumor tissue. In the authors' opinion, operation followed by radiotherapy are the procedures of choice.

*Brenner tumor.* For the sake of completeness this tumor may be mentioned since it falls in the group which has been designated as primary parenchymatous epithelial neoplasms of subsurface origin (Geist 1942).

The Brenner tumor is related to the other tumors in that it also arises from primitive epithelial cells which appear in the form of nests especially in the rete ovarii. They have been designated as Walthard's cells and are

probably a type of indifferent epithelial cell analogous to the type which produces the dysgerminoma. Its frequent association with other ovarian neoplasms (pseudomucinous and papillary serous cysts and fibroadenomatous tumors) suggests a derangement of growth of primitive ovary.

The tumors are solid or cystic, variable size, nodular, and are composed of branching strands of indifferent large cells containing glycogen. The arrangement is typical, the collections of cells being sharply demarcated from the dense collagenous connective tissue stroma in which they lie. Degeneration with liquefaction within the cell nests is common (fig. 11).

The Brenner tumor, although exceedingly interesting from a morphologic and genetic point of view, produces little effect upon the individual. There are no special symptoms other than those of the presence of a tumor. Usually it is discovered by accident. Menstruation is not affected nor does it produce any known endocrine change in the host.

It is entirely benign and although operative removal is indicated, conservatism should be practiced.

#### CONCLUSION

An attempt has been made to describe the neoplasms of the ovary which are associated with endocrine effects. That which is presented above represents a resumé of our knowledge at the present time. As has been stressed so frequently throughout this paper, considerable work remains to be done in order to clarify the subject. That certain tumors of the ovary can produce profound changes in the female as a whole has been definitely established. The *modus operandi* in all cases, however, is still far from clear. The advances that have been made in the field of endocrinology as it applies to the female have been gratifying but many questions remain unanswered. It is again suggested that hormonal studies of the individual harboring an ovarian neoplasm, both before and after removal, as well as on the tumor tissue itself, offer the greatest hope for enlightenment in the future.

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# Psychology of the Menstrual Cycle

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IN MANY primitive cultures menstruation has been ascribed to the cycles of the moon or tides. It has, moreover, been thought of as a dangerous condition requiring various taboos. Frazer in his 'Golden Bough' cites countless restrictions imposed upon the menstruating woman for the protection both of herself and the community. Even today there are cautions observed during the menstrual period which are directly descended from these earlier superstitions. The prohibition of bathing—originally intended to protect the local stream, used in common by the whole tribe, from contamination by menstrual blood—is a good example of such survival. In this sphere as elsewhere, however, knowledge gradually replaces superstition and physiology and psychology elbow out lunar myths and tribal taboos.

It is now well known that sex hormones follow a definite pattern in the menstrual cycle. While estrogen gradually increases with the ripening of the follicle and sharply drops off after the ovum is released, progesterone begins its upward course just prior to or at about the time of follicle rupture. In the event that pregnancy does not occur, the amount of the latter hormone likewise decreases about a week after its initial production. At the time of ovulation both hormones are, in the ordinary case, present to some extent. They are both at a minimum in the late pre-menstrual period.

Certain related facts of physiology are of interest. Among these are changes in basal metabolism and body temperature. Since the classic work of van de Velde (12) in 1905 it has been known that certain changes in temperature accompany the menstrual cycle. The body temperature is ordinarily at its lowest coincident with ovulation, when estrogen is maximum. As progesterone is produced the tempera-

ture gradually rises to a peak which roughly coincides with the maximum production of that hormone. The temperature then drops as progesterone decreases and continues downward as estrogen gradually increases. The question may accordingly be raised as to whether the term 'heat' as applied to estrus in the low animals may not also have its application to the human woman. Animals are maximally receptive to their mates during the period of 'heat' associated with ovulation. The human female seems not to be very different in this respect.

Present knowledge of the menstrual cycle distinguishes clearly between ovulation and menstruation. Until quite recently this distinction was not understood. The error resulted from the fact that estrus, or sexual receptivity and accompanying ovulation in the low animals is often characterized by a vaginal discharge readily confused with the menstrual flow of women.

The differentiation of ovulation and menstruation in a sense renders the term *menstrual cycle* a misnomer. Menstruation being a negative phase that occurs by default, the more appropriate designation would be *female sexual cycle*. The implication of this term is—rightly—that the 'aim of nature' is a positive one—menstruation taking place only when this aim is thwarted. This qualification being noted for subsequent elaboration, the more usual term *menstrual cycle* may for the present be kept. For the phases of the cycle, however, the terms pre-ovulative and post-ovulative, on the one hand, and pre-menstrual and menstrual, on the other, are used here throughout in order to emphasize appropriately the positive and negative aspects of the complete chain of events.

Fragmentary clinical information about the psychologic aspects of menstruation has been available. Chadwick (5, 6) well summarizes

es this knowledge. But for a systematic approach to the entire menstrual cycle the study made by Benedek and Rubenstein (3, 4) is outstandingly significant. Benedek, a psychoanalyst in Chicago, had under observation several neurotic women who regularly brought their dreams and discussed their problems. Her psychiatric colleagues supplied corresponding records for some of their patients. In this way the most intimate psychologic material accompanying 75 menstrual cycles in 15 patients became available. Rubenstein, a physiologist in Cleveland specializing in the endocrine aspects of the sexual cycle in women, independently studied a continuous series of vaginal smears made by the patients in question (after instruction by a woman physician) and of rectal temperatures taken simultaneously. On the basis of the psychologic observations Benedek completed presumptive calendars of the menstrual cycles. From the vaginal smears and body temperatures Rubenstein made similar predictions. When the two sets of tables were compared a high amount of agreement was found. A method for investigating the psychosomatics of ovarian function was thus established and revealed certain striking relationships.

The pre-ovulative phase of the cycle, with its rising tide of estrogen, is psychologically marked by strong heterosexual drives either overt or disguised. During this period the patients studied were found to be distinctly oriented toward men. Destructive trends—desires to injure or kill, as reflected, for example, in dreams—were noted, but the prevailing attitude was an outgoing orientation toward individuals of the opposite sex. With sexual gratification, the high tension of this period is relieved; otherwise tension mounted.

With the rupture of the follicle a relaxation of tension supervened, to be followed, as progesterone increased, by a passive receptive mood. A desire to be loved and possessed now came to the fore. Sometimes a conflict between the active heterosexual tendencies of the estrogenic phase and the more passive attitude of the early progesterone stage was observed. As estrogen sharply diminished and progesterone rapidly increased, a concentration of interest in the woman's own body became dominant.

Her dreams and fantasies reflected a desire to be nurtured and an attitude of self-nurture. With failure of fertilization and the decrease of progesterone, the passive-receptive attitude continued but pregnancy fantasies became prominent. A recurrence of heterosexual tension associated with the reappearance of estrogen was also occasionally found.

It is thus clear that the changes in sex hormone production are correlated with certain changes in psychologic orientation. Both together appear to have a bearing upon the biologic reaction of the organism at the periods in question. In the pre-ovulative phase of the cycle, when estrogen is increasing and the ovum is maturing, the chief business of the female would naturally be the acquisition of a mate. In the normal course of events this phase would presumably be over with the coming of ovulation. With the production of progesterone the uterus is prepared for the reception of the fertilized ovum and a more passive attitude would supervene. As the pregnancy preparation gradually increases during the post-ovulative phase the orientation might well become more and more a matter of nurturing. The ovum which is to be or has already been fertilized in the fallopian tube should soon be descending to the uterus where it will be implanted in the walls to grow and develop into a child. Consciously or unconsciously the woman would therefore at this phase be preoccupied with her own body—the nest of her offspring.

The pre-menstrual and menstrual phases which now supervene represent, as already noted, a negative adjustment that will not occur if fertilization has led to pregnancy. A minimal secretion of sex hormones is apparently the stimulus for the expulsion of the tissues, which, in the absence of fertilization, become waste. Psychologically the attitudes of the woman during this time are again adaptively characteristic. Pregnancy fantasies are not uncommon but regressive infantile sexual attitudes are also observed. 'Eliminative' psychologic trends become pronounced as seen, for example, in preoccupations about vomiting, oral or urethral discharge, abortion and bleeding. Emotional depression is prominent, especially in the transitional days, but the flow itself often brings a relaxation of tension.

Certain cautions are indicated. It must, for one thing, be noted that the attitudes depicted are by no means inevitable. They represent implicit rather than explicit orientations, not so much overt as potentially ready to seek expression at the first opportunity. The fluctuations above reported would hence seldom be recognized by the woman herself or most unprepared observers. This conclusion is strengthened by the fact that cyclic changes even when overt are of gradual occurrence and not easily detected. Furthermore, as in so many cases of unconscious attitudes, the environment usually offers sufficient 'excuse' to explain the mood or feeling of the moment; and the attitude itself, though perhaps basically prepared on other grounds or merely accentuated by the environmental occasion, is assigned completely to the latter. Not that these occasions are entirely negligible; they are in part fairly important in bringing out the prepared pattern of response. The more adverse the environmental conditions, the more extreme the reactions will be, in the determined direction. Again, it must be observed that these directions of response do not become crystallized with equal readiness in all women. Psychologically mature and well-adjusted women may resist them quite adequately and exhibit comparatively little fluctuation throughout the cycle. Such alterations would, on the other hand, be naturally exaggerated in neurotic individuals. The clarity of Benedek and Rubenstein's observations may perhaps be attributed to the fact that not only were their subjects neurotic but that the psychoanalytic method focusses on just those implicit attitudes which would otherwise escape attention.

The very recent study of Altmann, Knowles and Bull (1) confirms the picture above sketched. They found that before the onset of menstruation an outburst of physical and mental activity is characteristic and is paralleled by a corresponding peak during the ovulative phase of the cycle. The activity of the pre-menstrual phase was, however, associated with tenseness and irritability, sometimes depression, while that of the ovulative phase showed freedom from mental discomfort and generally bore the marks of elation.

The outstanding difference to be noted is thus the rather positive or progressive orientation in the ovulative part of the cycle as contrasted with the negative and regressive orientation characteristic of the menstrual segment. The difference appears not only in the physiologic production of sex hormones but equally in the psychologic attitudes of the woman.

The menstrual phases deserve further psychologic comment since considerably more is known about them than about the ovulative phases. The most general and outstanding action to the menstrual period is depression. Chadwick (5) has given an excellent summary of the mental status of this phase of the sex cycle. Tearfulness and anxiety, suspicion and tendencies towards self-pity or self-reproach are common features, in addition to a general feeling of low spirits and some irritability. Frightening dreams sometimes occur. Forgetfulness, obsessions, especially as regards cleanliness, and occasionally fantasies of pregnancy prevail. Supplementing these clinical observations are some statistical studies that may be cited. From the findings obtained by means of a questionnaire McCance, Luff and Widdows (10) have discovered that mental depression is at a maximum two days before a period, diminishes until the eleventh day, increases slightly up to the seventeenth, diminishes to the twentieth, and finally increases. By a similar technique Conklin, Byrom and Knipes (7) found that the characteristic orientation during the menstrual period is introverted, i.e. one in which the subject turns in upon herself instead of engaging in outward-going activities. Perhaps the most interesting investigation along the present lines is that of Balazs (2). From a study of 3110 cases of suicidal attempt, he discovered a trend which may be summarized in the following index figures: menstrual: 4.7; post-menstrual: 4.2; intra-menstrual: 3.3; pre-menstrual: 2.8. Balazs indicates that his results contradict those of previous investigators, e.g., Krafft-Ebing, who regarded the pre-menstrual period as the most hazardous from the standpoint of suicidal attempt. However, his data are easily reconciled with the rest if one notes that while a maximum depression may occur in the late pre-menstrual

case, suicidal attempts may most commonly be precipitated on the first day of menstruation, an end result.

The state of affairs in the organism at the menstrual period is more complex than during earlier phases of the cycle. While ovarian deficiency can not be overlooked in attempting to explain the feelings of low energy and irritability of which women complain at this time, the hormones alone are insufficient to account for all that happens. According to Hoskins (8), 'Menstruation . . . marks a frustration of nature—the acknowledgement of failure of fertilization.' This total biologic context must be carefully considered if justice is to be done to the various features of the woman's reaction. Metchnikoff (11) long ago pointed out that menstruation is in a sense abnormal. It would not occur if pregnancy had taken place as nature 'intended.'

The first and most obvious aspect of the frustration which the menstrual flow implies concerns the fate of the ovum itself. Although prepared for fertilization, the ovum has not been fertilized. The hormones keep pace with this negative outcome. Progesterone decreases markedly while estrogen is also waning. The menstrual flow is apparently set off by the regression of the hormones as a stimulus.

A second aspect of the reaction to frustration which is involved concerns the appearance of blood. To the primitive mind, and even to many civilized individuals, blood is naively taken as a proof of guilt and death. Thus, to a girl who has not been prepared for menarche the sight of the first menstrual blood may evoke fear and shame. The 'affliction' may even be regarded as punishment for secret sins like masturbation. Such an attitude on the part of the woman is complicated further by the social taboos which, as already mentioned, have from earliest times surrounded menstruation. It has, for instance, been believed that if a menstruating woman walks through a field of wheat the crop will be ruined. Similarly, it is thought even today by some individuals that flowers will wither if worn during menstruation. In many primitive tribes women have accordingly been segregated as an initiatory rite at puberty and regularly thereafter during the monthly

periods as a protective measure. The effect of such treatment on the woman herself is not difficult to imagine. The inferiority and guilt feelings which the flowing of the blood alone suggests is strongly enhanced. These effects of social conditioning when added to the psychologic correlates of the abortive endocrine process not unnaturally make for the depression and irritability observed in women just before and during the menstrual period.

The above is obviously a paradigmatic schema only. A particular woman will never do more than approximate it. But on the evidence now available the picture holds for the typical case if carefully observed. The extent to which it may be modified by individual differences in endowment and experience is nevertheless very great. Thus certain attitudes toward menstruation may be taken over by the young girl through imitation or identification. It has often been observed clinically that whether or not a girl is unduly disturbed or fatigued or whether she goes through the menstrual period quite normally is correlated with similar attitudes on the part of the older women in her environment. Of similar interest are the more transient effects of current emotion on menstruation.

No account of the psychologic factors involved in the menstrual cycle would be complete without some recognition of the part which the climacteric plays as related to earlier menstrual symptoms. Something in the nature of an analogy is here in order. Just as the early adolescent period, when menstruation has just begun, may be thought of as corresponding to the active heterosexual stage which is found in the pre-ovulative period of the menstrual cycle, so, proceeding with the analogy, the adjustment of the mature maternal woman corresponds to the more passive and receptive orientation of the ovulative and post-ovulative stages. Finally, the menstrual period itself would be paralleled, as a frustration of nature, by that frustration on a grander scale which is ushered in by the menopause. Whereas the menstrual period represents a failure of fertilization in an individual cycle, the menopause represents the failure of the whole life cycle in respect to procreation. Any symptoms which

might have been present as a reaction to frustration microcosmically during earlier menstrual periods might thus very naturally be found in exacerbated form on the macrocosmic level of the menopause. The common occurrence of involutional psychoses in women can hence be appreciated. From a similar standpoint to that here adopted in interpreting the menstrual phase of the monthly cycle, Malamud, *et al.*, (9) in a recent discussion of involutional psychosis have maintained that the withdrawal of hormones is but one aspect of a more general psychobiologic frustration.

#### SUMMARY

If one examines the female sexual cycle as a whole, the following condensed picture thus seems to emerge on the basis of what is at present known about physiologic and psychologic interrelationships. In the pre-ovulative phase, when estrogen is being produced in increasing amounts, an active heterosexual trend is predominant. The post-ovulative phase, in which progesterone is secreted, is accompanied by a shift of attitude. Interest is now more apt to be centered in the woman's own body. Both phases seem psychologically to have a forward-looking character. The pre-menstrual phase, which already signalizes the failure of fertilization, radically alters the picture. While on the physiologic side sex hormones are now at their lowest titre, on the psychologic side, 'eliminative' and 'cleansing' trends appear. Attitudes of inferiority and guilt may be present. As a compensation, fantasies of pregnancy may occur. With the actual onset of menstruation and during the flow, a sense of depression, sometimes expressed as irritability, is not uncommon. This type of response becomes intelligible if the menstrual flow is regarded as the

result of a biologic frustration to which the woman is reacting psychologically as well. But as estrogen begins once more to increase with the beginning of a new cycle, a more positive orientation supervenes. All in all there could hardly be a more dramatically revealing demonstration of the unity of psyche and soma. As a problem in psychosomatic medicine the relationships here in question are rich in possibilities for future research.

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## THE URINARY KETOSTEROIDS—REPORT OF CONFERENCE<sup>1</sup>

WITH THE DEVELOPMENT of microchemical methods for the extraction and determination of urinary steroids, numerous attempts have been made to determine the physiologic and clinical significance of the excretory levels, particularly of the 17-ketosteroids. Such difficulty has been encountered in comparing data from different laboratories due to variations in the methods of extraction and determination employed. In an attempt to secure some agreement on essential technical methods and to initiate discussion of general interpretations and results, the Josiah Macy Jr. Foundation called together for a conference on June 7, 1942 a group of active investigators in the field under the chairmanship of Dr. Elmer Sevringhaus.<sup>2</sup> A summary of the findings of this conference is presented here in the hope that endocrinologists generally may be benefited. A large body of useful data and opinion was made available by the individual conference members. In representing this abstract of it the writer wishes at once to absolve the individual conference members from responsibility for any sins of interrelation that may be his doing.

The principal 17-ketosteroids that have been isolated from human urine and identified chemically are androsterone and two of its isomers, isoandrosterone and etiocholanol-3 $\alpha$ -17-one; dehydroisoandrosterone; androstenone-17;  $\Delta^{3,5}$  androstadienone; and estrone. Estrone is an estrogenic phenolic steroid that is usually separated by extractive processes from the other 17-ketosteroids listed. These latter are all considered

androsterone derivatives (having 19 carbon atoms in the typical steroid skeleton) and have been loosely called the urinary 'androgens.'

In urines of normal men and women, androsterone and etiocholanol-3 $\alpha$ -17-one are the principal 17-ketosteroids and are sometimes called the  $\alpha$ -17-ketosteroids; they cannot be precipitated from solution by digitonin. Isoandrosterone and dehydroisoandrosterone are the urinary  $\beta$ -17-ketosteroids; they are digitonin-precipitable and are present in normal urines in smaller amounts. Androstenone-17 and  $\Delta^{3,5}$  androstadienone are non-alcoholic 17-ketosteroids, and only the former has hitherto been isolated quantitatively (but in small amount) from normal urine.

The  $\alpha$  and  $\beta$ -ketosteroids are not excreted into the urine to any extent as free compounds, but as esters. The recent work of Venning and of Gallagher indicates that these are sulfuric acid esters. The chemical extraction of these sulfates is a laborious and difficult procedure. An hydrolysis of the urines containing them is therefore practiced, since the free steroids are easily extractable with organic solvents. Strong mineral acids, such as HCl or H<sub>2</sub>SO<sub>4</sub> are added to fresh urines and the practice is to heat (with or without refluxing) to boiling for a short period of time. The procedures using HCl are as follows: a) boiling for 7 to 10 minutes with 10 to 15 per cent HCl by volume added to the urine; b) refluxing for one hour after addition of 4 per cent HCl by volume. Alternatively, H<sub>2</sub>SO<sub>4</sub> is added to 5 per cent by volume to urine and boiled for 15 to 30 minutes. There is some reason to believe that the non-alcoholic 17-ketosteroids may arise as a result of the hydrolytic procedure (e.g., androstenone-17 from androsterone and its isomers  $\Delta^{3,5}$  androstadienone from dehydroisoandrosterone).

The organic solvents employed for extracting the 17-ketosteroid from urines are those immiscible with H<sub>2</sub>O; the principal ones now in use are ethyl ether, benzene, toluol and carbon tetrachloride. These extractives may be employed after the hydrolized urines have been rapidly

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cooled or may be circulated in an extraction apparatus during the urine hydrolysis. When simultaneous hydrolysis and extraction are employed, benzene, toluol and carbon tetrachloride are the usual extractives, and the solvent is circulated from 3 to 4 hours. When it is desired to extract urinary estrogens as well as the 17-ketosteroids, carbon tetrachloride should be avoided as it is a poor solvent of estrogen. Ethyl ether appears to be the best general steroid extractive, but it should be free of organic peroxides, and because of its explosive qualities should not be used in a mechanical extractor.

The lipid material extracted from acid-hydrolyzed urines contains organic acids, various pigments, the neutral urinary steroids and phenolic substances. A number of non-steroidal substances, including acids and certain pigments, may be removed by washing the organic solvent with  $\text{NaHCO}_3$  and  $\text{Na}_2\text{CO}_3$ . The phenols (including the urinary estrogens) may then be removed by strong alkali (1N to 5N NaOH is usually used). The organic solvent remaining (washed free of alkali with  $\text{H}_2\text{O}$ ) contains neutral lipids, including the neutral 17-ketosteroids. This 'crude neutral' fraction is the one employed either for androgen or total 17-ketosteroid assay or for further extraction. The crude neutral fraction should not be kept in solution if it is to be held for later assay, but should be kept dry after evaporating off the solvent.

The crude neutral fraction may be assayed for total androgenic activity by administration to test animals. The assay result obtained will depend largely on the nature of the androgenic steroids present. The i.u. of androsterone is 0.10 mg. In the assay using the baby chick, for example, 0.10 mg. of isoandrosterone is equivalent to 0.12 i.u. of androsterone; etiocholanolone, to 0.00 i.u. (i.e., inactive); dehydroisoandrosterone, to 0.33 i.u.; androstenone, to 0.08 i.u. (Dorfman).

For quantitative determination of 17-ketosteroids, various modifications of the colorimetric reaction of m-dinitrobenzene with ketones in alkaline solution have been employed. This reaction, originally described by Zimmerman, involves the development of a pink color (having an absorption maximum at  $520 \mu\mu$ ) by the 17-ketosteroid. When the reaction is applied to the crude neutral fraction of urine, the typical pink color is in part obscured by other colors that develop simultaneously. The presence of the atypical colors leads to an over-estimate of the 17-ketosteroids present. To obviate this over-estimate, certain color correction equations have

been suggested (Fraser, *et al.*, *J. Clinical Crinology* 1: 234. 1941; Talbot, *et al.*, *J. Chem.* 143: 211. 1942) which, on certain assumptions, purport to correct for the chromogen is not 17-ketosteroid. Since much of the at chromogen is non-ketonic, micro-methods have been devised which make possible the separation of the ketones of the crude neutral extract from the non-ketonic material (Talbot, *et al.*, *J. Chem.* 136: 365. 1940; Pincus and Pearlman, *Endocrinology* 29: 413. 1941). The Zimmerman reaction is then applied to the neutral ketone fraction. Methods for removing interfering chromogen by adsorption have been suggested by several investigators (e.g., Baumann and Miller, *Endocrinology* 27: 664. 1940), but the possibility of non-specific adsorption must be avoided.

The two current modifications of the Zimmerman reaction differ in that one involves the development of color in an aqueous alcoholic solution of the reagents, whereas in the other absolute alcohol is used as the solvent. According to Nathanson (in press) the two methods can be brought into good agreement if sufficient time for color development be allowed in each. In the absolute alcohol method, urinary extracts (at  $25^\circ\text{C}$ .) develop full color in 80 minutes, whereas in the Holtorf-Koch aqueous alcohol method 105 minutes are requisite (*J. Biol. Chem.* 135: 377. 1940).

Two other methods for the determination of urinary 17-ketosteroids are available. Of these, one is colorimetric and involves the development of a blue color by the application of  $\text{SbCl}_3$  to neutral ketonic extracts of urine (Pincus, *Endocrinology* 32: 176. 1943). It appears to be more specific than the Zimmerman reaction, but dehydroisoandrosterone is only feebly reactive. More specific is the polarographic method (Weintraub *et al.*, *J. Biol. Chem.* 136: 653. 1940) which requires the application of a ketone reaction. The polarographic method requires expert handling of delicate physical apparatus. If ketosteroids other than the 17-ketosteroids (e.g., 3-ketosteroids or 20-ketosteroids) are present in urine extracts, they will contribute to the Zimmerman titer in both crude neutral and ketonic neutral fractions, especially in pregnancy urines which contain large amounts of 20-ketosteroids (e.g., pregnanolone, epi-allopregnanolone, allopregnanolone). The  $\text{SbCl}_3$  reaction largely excludes such compounds, but the 20-ketosteroids may complicate the polarographic method.

The identification of specific urinary ketosteroids requires the application of methods of chemical isolation and can be conducted

with large quantities of urine. For routine work the separation of various groups of substances may be affected. Thus the  $\beta$ -ketosteroids can be separated from the  $\alpha$ -ketosteroids by digitonin precipitation (Talbot, *et al.*, *J. Biol. Chem.* 136: 35, 1940; Baumann and Metzger, *Endocrinology* 7: 664, 1940). The alcoholic (hydroxylated) ketosteroids can be separated either by the application of succinic anhydride (Pincus and Pearlman, *Endocrinology* 29: 413, 1941) or by adsorption (Talbot, *et al.*, *J. Biol. Chem.* 139: 521, 1941). It is desirable that assays be made directly on the separated fractions. The significance of quantitative variations in various fractionated 17-ketosteroids remains yet to be determined. Similarly the presence of varying quantities of androgenically active ketosteroids requires further elucidation.

The determination of 'normal' values for urinary 17-ketosteroids has been complicated by variations in methods of extraction and assay. There appears to be a definite diurnal rhythm in both men and women (Reifenstein, *et al.*, Pincus, *Clinical Endocrinology* 3: 195, 1943) of such a nature that the lowest values are obtained for the period of sleep. The diurnal rhythm may be ruled out by taking full 24-hour samples. Even in such specimens marked individual differences appear which cannot always be attributed to such factors as age, weight, or other obvious physical factors. Children below the age of 6 excrete very small amounts of neutral 17-ketosteroids (0.1 mg. per 24 hours) with increasing

excretion from 6 to 18 years when a more or less characteristic level is attained. There appears to be a decline in excretion in extreme old age. Among normal mature persons there is a sex difference (but with considerable overlapping). Twenty-four-hour values for women vary from 5 to 18 mg. when the Zimmerman reaction is applied to the crude neutral fraction, 3.5 to 15 mg., respectively, on its application to the ketonic neutral fraction. Corresponding values for men are 7 to 27 mg. and 5 to 23 mg., respectively. The alcoholic ketosteroids contribute from 50 to 85 per cent of these titers, the  $\beta$ -ketosteroids seldom exceed 15 per cent of the total titer and are ordinarily 2 to 3 per cent of the total.

Significant increases above normal have been encountered in cases of adrenal hyperplasia or adreno-cortical carcinoma (though exceptions to the latter have been noted) and in liver cirrhosis(?). Significantly low levels of excretion have been regularly encountered in Addison's disease and hypothyroidism. In conditions ranging from the common cold to almost any surgical intervention, marked temporary declines in urinary 17-ketosteroid excretion occur. The significance of these and numerous other variations in 17-ketosteroid excretion requires further investigation.

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## EFFECT OF TISSUE INJURY ON THE BLOOD SUGAR LEVEL IN DIABETES MELLITUS

IT HAS long been known that the hyperglycemia and glycosuria of the diabetic patient are accentuated by inter-current infection or trauma and that increased amounts of insulin are commonly needed to keep the patient in equilibrium under such circumstances. The mechanism through which the hyperglycemic effect is produced has remained until recently, however, a matter concerning which even plausible theory has been lacking. The problem has been under study by Menkin<sup>1</sup> during the past two years and data are now at hand for an explanation of the phenomenon.

Comparative observations were made on non-diabetic dogs and those which had been subjected to destruction of the pancreas. The method was to inject turpentine into the pleural cavity and withdraw the exudate for analysis for certain of its relevant constituents. These included sugar, total proteins, urea and lactic acid. By determining the same materials in the blood, any significant gradients as between the two sites could be recognized. In the control dogs, within the first few hours of the induced inflammation, the concentration of glucose in the exudate proved to be higher than that in the blood stream. The increased level of exudate sugar, however, was not sustained but soon dropped as low as, or even lower than, that of the blood sugar. Re-injection of the irritant induced a second rise in the blood sugar but this was also

transient. Since at times definite elevation of blood sugar occurred, the increase in the exudate could be ascribed in such instances to seepage from the blood into the irritated tissue. That this is not the whole explanation, however, is evident from the fact that the hyperglycemia was or transient whereas the augmented exudate sugar persisted. In contrast with the evanescent rise in the blood sugar of the normal dogs, the effect of similar inflammation in the diabetic subject proved to be greater and longer sustained.

One possibility in explanation of the phenomenon would be that some of the turpentine had been resorbed from the pleural cavity and carried to the liver, thus bringing about augmented hepatic glycogenolysis. Since, however, the turpentine-induced inflammation was not accompanied by changes in the glucose-tolerance curve, as does occur after liver injury, Menkin regards that explanation as inadequate. He emphasizes the fact that throughout the duration of the inflammation the exudate sugar of the diabetic animal remains consistently at a higher level than does the blood sugar, and this in spite of the fact that glucose is extremely diffusible.

The explanation that best seems to fit the facts is, as Menkin says, that constant new formation of sugar occurs at the site of the tissue injury. A concomitant rise in the urea concentration of the exudate suggests that the source of the newly formed sugar is protein. It is the diffusion of the newly formed glucose into the circulating blood from the site of tissue injury that enhances the diabetic condition.

R.G.H

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<sup>1</sup> MENKIN, V.: Gluconeogenesis and cellular injury. A further inquiry into the mechanism involved in diabetes enhanced by inflammation. *Am. J. Physiol.* 138: 396. 1943.



## HORMONE FACTORS IN LIBIDO

LIBIDO or amorous desire in the human being is a complex function in which anatomic, physiologic, neurologic, hormonal and chologic factors all play determining parts. <sup>1</sup> tes of ill health aside, libido is either present easily aroused in men at all times during the reductive period of life, whereas in women it much less constantly experienced. That detection of the primary sex glands results in complete loss of libido is widely believed, but this is not necessarily the case in either men or women.

Strictly speaking, since libido is a subjective emotion, it can be studied convincingly only in human beings. To what extent arousal of mating behavior in infra-human forms can be equated with libido must remain conjectural, though 'lingness' or 'unwillingness' to mate certainly suggests the presence or absence of 'desire'. In many animals, the female of the species will receive the male in coitus only when in heat or estrus and this is timed with follicle maturation. In many animals there is evidence that the administration of estrogenic substances to castrated males or to intact females outside of the mating season will awaken sexual receptivity. The period of heat in the bitch lasts for a little longer than a week and occurs at 6 month intervals. The administration of fairly large doses of pregnant mare's serum or of combinations of pregnant mare's serum and chorionic gonadotropin to bitches is capable of inducing estrus-like changes several months before the expected estrus so that in some instances the male will be received in heat. <sup>2</sup> The follicle stimulating effect of the gonadotropins not only increases estrogen production but probably accounts indirectly for minute amounts of progesterone. In the induction of sexual receptivity in the castrated guinea pig or rat it has been said that not only the estrogenic hormone but also progesterone is necessary. <sup>3</sup> Young and his collaborators <sup>4</sup> obtained more frequent and more normal responses in castrated guinea pigs if a little progesterone supplemented the course of estrogens.

The cycle of the female chimpanzee simulates

that of the human female. Unlike the latter, however, the chimpanzee will accept the male only during the height of genital turgescence, which corresponds to the phase of follicle maturation. During the luteal phase, regressive changes set in, at which time the female will fight off the male. It may be said insofar as estrus is concerned, that the corpus luteum hormone has an action opposite to that of estrogens. This fact receives further corroboration in the work of Gillman <sup>5</sup> who has shown that the perineum of the baboon is a sensitive indicator in experiments involving the use of female sex hormones. Deturgescence in the normal adult female baboon is a positive phenomenon, due to the presence of progesterone and not to the absence of estrogens. Progesterone administered in total doses of 10 mg or less will cause depression of the turgescence of perineum.

In case of the human species certain females exhibit even nymphomaniacal tendencies during the weeks before the onset of menses. These same individuals frequently show evidence of premenstrual tension. Endometrial biopsies often reveal imperfect progestinal types of endometrium and the blood estrogen titers may be somewhat higher than normal. It may be that in these cases excessive estrogen over rides corpus luteum activity. A high threshold in the kidney for estrogen excretion may be the prime fault. Following the administration of parenteral progestins to these women in doses of 1 to 5 mg every 3 to 7 days or oral progesterone in 5 mg doses during the last half of the menstrual cycle, there is frequently noted a detumescence of the sexual urge. <sup>6</sup>

Although estrogens have been administered with resultant increase in libido, nevertheless many women without sexual desire fail to respond to even massive doses. The addition of small amounts of progesterone to the estrogen therapy or the administration of gonadotropins have evoked in some instances more satisfactory results in these patients in whom estrogens alone proved futile. More consistent results, however, are obtained with continued androgen therapy. Seventy five to 200 mg of testosterone propionate has frequently proved aphrodisiacal. Information as to the status of the sexual libido before and

<sup>1</sup> GREENBLATT R B *J Am Med Assoc* 121 17 1943  
<sup>2</sup> GREENBLATT, R B, AND F R PUND *South M J* 34 1941

<sup>3</sup> ALLEN W M. In discussion of paper by Greenblatt.  
<sup>4</sup> YOUNG W AND OTHERS. Quoted by G W Corner. *The Hormones in Human Reproduction*. Princeton University Press 1942, p 97

<sup>5</sup> GILLMAN J. *Endocrinology* 26 1072 1940

<sup>6</sup> GREENBLATT R B, F MORTARI AND R TORPIN. *Am J Obst & Gynec* 44 658 1942

after implantation of pellets of testosterone propionate in dosages varying from 25 to 400 mg. was obtained from 55 women.<sup>1</sup> It was learned that restoration of libido readily occurred following implantation in those women who at some time had known libido. Many married women volunteered the information that the loss of sexual desire led to marital discord. Following pellet implantation there was a return of coital pleasure, which often terminated in orgasm. A reawakened interest on the part of the husband usually followed and husband and wife once more fell in love. Among those women who had a strong to moderate degree of sexual desire before implantation, either no significant change or further increase in sexual pleasure was noted. Two women with normal libido had a temporary decrease in sexual desire for several weeks immediately after pellet implantation and then a resurgence of the libido to a greater degree than that before the implantation. In several instances it was noted that the libido returned to the pre-implantation status by the end of the third to eighth month. In the majority, however, it persisted long after the pellets had been absorbed. In 3 women who had never experienced sexual desire no change was noted. Salmon and his associates<sup>7</sup> have studied the effects of testosterone propionate on the sexual reaction of women and concluded that androgens *a*) cause a heightened susceptibility to psychic and somatic sexual stimulation, *b*) produce an increased sensitivity of the external genitalia, and *c*) induce a greater intensity of sexual gratification.

The increase in libido in the woman following the administration of chemically pure androgenic substance in one form or another, must be the result of a specific pharmacologic effect. The action may be mediated through minor changes in electrolyte balance or the effect may be directly on specific organs. Hartman<sup>8</sup> noted that testosterone invariably had an estrogenic action on the sex skin of the female monkey. The sex skin was always brilliant red. In this respect he found progesterone antagonistic to estrin. Testosterone did not antagonize the action of estrogens. Even in pregnant macaques Hartman was able to blanch the sex skin with a sufficiently high dosage of progesterone. However, the concurrently injected estrogens and testosterone or

both were sufficient to over-ride the blanching action of the progesterone.

Large doses of progesterone when administered parenterally or orally in the form of a hydroxyprogesterone frequently have a depressing effect on woman's sexual desire. Repeated doses of desoxycorticosterone, like progesterone, also proved anaphrodisiacal. In a series of 23 women in whom pellets of progesterone were implanted for various gynecic disorders it was noted that in over one-half there was a decided depression of the sexual libido. This was particularly clear cut in several in whom sexual libido had been markedly exaggerated. Two patients, however, volunteered the information that the libido had increased.

In an ovariectomized woman of low intelligence, poor breeding and uninhibited instincts several instructive observations were made. Some time after castration she complained of marked decrease of sexual desire. It was found that libido was greatly heightened following the ingestion of alcoholic liquors or after the administration of courses of either estrogens or androgens. The administration of progesterone, however, caused a marked slump in libido, leaving her sexually non-receptive. When pellets of 30 mg. of estradiol and 50 mg. of progesterone were implanted simultaneously libido was greatly enhanced.

From the inconsistent evidence now available a final over-all appraisal of the precise significance of hormonal factors in libido cannot be offered. Human behavior involves all sorts of mental processes not subject to experimental control. In women with normal libido, sexual gratification may depend mostly on the proper 'amatory prelude' or on the proper mechanics of coitus.<sup>9,10</sup> Sufficient evidence has accumulated to show that the administration to women of estrogenic and particularly androgenic substances in sufficient dosage may increase or awaken libido and that chemically pure progesterone and desoxycorticosterone in large dosages may suppress sexual desire. Altogether, it appears, then, that sexual libido is a phenomenon depending in part but not entirely upon well defined chemical substances.

R.B.G.

<sup>7</sup> SALMON, U. J.: In discussion of paper by Greenblatt<sup>1</sup>.

<sup>8</sup> HARTMAN, C. G.: *Endocrinology* 26: 449. 1940.

<sup>9</sup> KELLY, G. L.: *Sexual Feeling in Woman*. Kingsport, Tenn. Kingsport Press, 1930.

<sup>10</sup> HUHNER, M.: *Sexual Disorders*. F. A. Davis Co., Philadelphia, 1942.

# CURRENT ENDOCRINE LITERATURE

BY: DANIEL A. MCGINTY. Collaborators: ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, RAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLIN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST JOHN, CHARLES W. TURNER, ERICH VON HAAM, HAROLD WOOSTER.

## BOOK REVIEWS

IGELER, W., AND U. L. TORRES.

as Relações da Osteodistrofia com a Hipertrofia das Paratiroides e Insuficiência Renal Contribuição ao estudo das molestias osseas e lepra) (With Summary in English). *Emenda Grafica da "Revista dos Tribunais" TDA, São Paulo, 1942.*

The authors introduce the work with a discussion of two of the most important skeletal disorders, osteitis deformans (Paget's) and generalized osteitis fibrosa (v. Recklinghausen's). The remainder of the book is concerned with the histology and function pathology of the parathyroid glands. New investigations by the authors led them to the conclusion that parathyroid hyperplasia is commonly an adaptive reaction to various disturbances elsewhere, and especially to the kidneys. It was found that induction of osteitis by the agency of metallic salts and acids causes first chronic renal insufficiency followed by the skeletal changes. Similarly, clinical renal injury and especially that seen in nephrosis is accompanied by similar change in the parathyroids, the degree of kidney disturbance and of the alteration running parallel. The association is mediated through the parathyroid glands.

The book is well printed and fully illustrated with excellent original photomicrographs.—R.G.H.

EVES, N.

As Adrenais Na Fisiologia Sexual, *Imprensa Industrial, Recife, 1942.*

The author presents a timely discussion of the relationship of the adrenal glands to the determination of sex and the endocrine functions of the gonads. The topic is treated systematically, considering the evidence at various levels, the embryologic and histologic, and physiologic and clinical. A closing bibliography is made up of over 200 citations.—R.G.H.

## ADRENALS

PATTERSON, J., I. M. MCPHIE AND A. W. GREENWOOD.

17-Ketosteroid excretion in adrenal virilism. *Brit. M. J.* 1: 35. 1942.

All cases of adrenal tumors and of primary virilism showed very high excretions of 17-ketosteroids and it was not possible to distinguish between adrenal hyperplasia and adrenal tumors before puberty on the basis of urinary excretion values. In secondary virilism only half of the patients showed increased 17-ketosteroid excretion rates, the others being normal. Three cases of feminism showed low ketosteroid excretion rates—D.A.M.

SEMME, W.

The effect of adrenal cortical hormone (desoxycorticosterone acetate) on the blood composition in toxic diseases. *Ztschr. kinderh.* 62: 65. 1940.

Administration of desoxycorticosterone acetate to patients with severe toxic forms of diphtheria, scarlet fever and dysentery had no influence on the increased blood potassium or decreased blood sodium and chloride nor on the clinical course of disease.—D.A.M.

WILSON, A.

Sublingual desoxycorticosterone acetate in Addison's disease. *Lancet* 242: 762. 1942.

In 4 patients with Addison's disease, administration of 10–20 mg. per week of desoxycorticosterone acetate intramuscularly brought about satisfactory results. In the same patients, daily sublingual administration of 10 mg. in propylene glycol failed to maintain a satisfactory state.—D.A.M.

## ENDOCRINE GENERAL

BENJAMIN, H. R., AND A. A. WEECH.

Basal heat production in relation to growth. A longitudinal study on normal infants six to twenty months of age. *Am. J. Dis. Child.* 65: 1. 1943.

A total of 217 observations, covering the entire age span, were made on two infants, and 40 additional observations covering shorter periods were obtained on two other infants. An open-circuit-type chamber calorimeter was used. Large day to day fluctuations in the basal heat production of individual infants were observed, with greater variation in a given infant during the early months of life. In terms of the coefficient of variation the fluctuations amounted to 9 per cent, as compared with a reported 5 per cent for adults. In relation to growth, the association between total calories and body weight was the closest, and there was no evidence of change in the calories produced per kilogram with advancing age. In contrast, there was a definite change with growth in the heat production per unit of surface area or per unit of height. However, the quantity of heat produced per kilogram of body weight varied significantly in different infants of the same age. Day to day fluctuations limit the accuracy with which basal heat production can be predicted from measures of growth. Over the age span studied, prediction on the assumption of a constant heat output per kilogram of weight is not significantly less accurate than prediction on the basis of regression equations. For this study and in other reported studies there was found a range of 11.3 to 13.7 per cent in the total error of prediction, composed of variability among different infants (6.5 to 9.8 per cent), and longitudinal variation in the individual infant (5.5 and 10.3 per cent). No evidence was adduced that the excess heat production per kilogram of tissue of the infant over that of the adult is due to the normal changes in the rate of growth.—*E.C.R., Jr.*

BURROWS, H., D. H. MACLEOD AND F. L. WARREN.

Excretion of ketosteroids in human pregnancy urine in relation to sex of the fetus. *Nature, London* 149: 300. 1942.

Ketosteroids were estimated colorimetrically. Results were not conclusive. Although women bearing male feti excreted more ketosteroids, there was a wide range of individual values.—*D.A.M.*

CAMERON, D. E., D. MELE, H. S. HIRST AND F. FELDMAN.

Abnormal brachial blood pressure response to postural change in patients suffering from psychoses of the senium. Control by thyroid. *Psychiat. Quart.* 17: 67. 1943.

Forty-one senile patients and 16 normal controls were tested on a tilt-board for circulatory compensatory efficiency. The scores of the seniles were markedly inferior to those of the control subjects. Ten of the patients were treated with desiccated thyroid substance, 3 grains daily. In 7 of these the compensatory efficiency was improved.—*R.G.H.*

DRIPS, DELLA G.

Relation of sex hormones to the climacteric. *Jour. Lancet* 62: 437. 1942.

A review.

DICKINSON, R. L.

Gynecology and psychiatry. *Bull. Menninger Clin.* 7: 3. 1943.

The author contributes a brief introduction to a number of the Bulletin that is devoted exclusively to psychological and psychiatric aspects of gynecology and obstetrics. He emphasizes the need for more intensive attention to the psychosomatics of these subjects.—*R.G.H.*

DIAZ MINDURRY, EUGENIO F.

Hormone treatment of nervous heart disease. *Semana méd.* 49; ii: 1230 (1942).

A few cases are reported of cardiac disturbances of indubitably neurotic character in which the neurosis was based on endocrine disturbance. The general symptoms were usually tachycardia, palpitations, extrasystoles, precordial pain. One patient developed these symptoms after taking the care of her mother, suffering from heart disease, and copied her complaints. The treatment, more or less successful in every case, consisted in the case of artificial menopause, in estrogens; in stilbestrol, in premenopause with myoma of the uterus and a tendency towards hypermenorrhea; in testosterone, in amenorrhea, estrogen and desoxycorticosterone and in a mild hyperthyroidism secondary to a moderate hypogonadism with diiodotyrosine, and insulin; the latter later substituted by estrogens.—*J.E.M.*

GERALD, J E, AND AUGUSTA WEBSTER

Obstetric significance of barbiturates and vitamin K *J A M A* 119 1082 1942

In a series of over 600 cases in the Cook County Hospital, Illinois, it was found that the administration of vitamin K, either the original alfalfa extract or the synthetic product, to a mother in labor increases the percentage of prothrombin of both mother and child. The vitamin may be given either orally or parenterally. Such medication also prevents the drop in the prothrombin level of the baby which normally occurs in the second to the fifth day. The administration of sodium pentobarbital or sodium amyl amobarbital as an anesthetic definitely increases the prothrombin level in mother and child. The decrease can be prevented by the administration of vitamin K to the mother during labor. It is apparent that even small doses of barbiturates affect the prothrombin level—C P

ANKEL, L

Endocrinology and the specialties *Rev med de Rosario* 32 1002 1942

Endocrinology as a clinical specialty is discussed in regard to its development and relation to internal medicine, obstetrics and gynecology

ELL, M G

Functional disturbances of menstruation *Bull Menninger Clin* 7 6 1943

The psychological meaning of menstruation is discussed in the light of folk superstitions and current misapprehensions. The psychological etiology of many cases of amenorrhea and dysmenorrhea is pointed out and various cures by psychotherapy are mentioned. It is emphasized that the gynecologist must, for the most part, serve as his own psychiatrist and that, as such, he can frequently do much to ameliorate menstrual disorders—R G H

OSKINS, R G

Psychosexuality in schizophrenia—some endocrine considerations *Psychosom Med* 5 3 1943

Numerous features of the schizophrenic psychosis point to an immature level of psychosexual functioning. The question is raised whether this is due to deficiency of sex hormone. It is pointed out that sexual behavior in animals is largely determined by this factor. Mating activity can

be prevented by castration and precocious sex behavior can be induced by the use of primary sex hormones. The schizophrenic patient, however, usually has normal genitalia and probably excretes sex hormone in an approximately normal amount. Furthermore, castration in human beings seldom if ever gives rise to schizophrenia nor does that operation have much influence on the psychosis if performed after its development. Although quantitative alterations in the sex hormone titre show little correlation with the psychosis it is theoretically possible that variations in responsiveness to the hormones might be a factor. That such responsiveness varies widely under different conditions is well known. Dissociation between the somatic and the psychodynamic reactions to sex hormones is also possible under numerous conditions, e.g., precocious puberty in boys and girls is commonly not accompanied by much eroticism. Dissociation between sex hormone production and mating response can be demonstrated experimentally by the induction of lesions in the hypothalamus. Another theoretical possibility is that schizophrenia might be induced by imbalance in the titres of circulating androgen and estrogen as homosexuality is believed by some to be produced. This possibility is controverted by the infrequency with which administered sex hormone benefits homosexuality and by the fact that acquired sex reversal in man does not lead to schizophrenic symptomatology. Whether or to what extent schizophrenia might be due to qualitative abnormalities of sex hormone production is discussed. Evidence is cited that certain animals are more responsive in terms of sex behavior to stallion urine extract than to testosterone. Evidence of aberrant sex hormone production in man is, however, lacking. Likewise lacking is evidence that the psychosexual perturbations of schizophrenia might be due to abnormalities in the metabolism of normal sex hormone. It seems probable that the psychosexual disharmony of schizophrenia is not to be ascribed therefore to immediate abnormality in either amount, balance or chemical nature of the sex hormones. The possibility remains that abnormal responsiveness to these hormones might account for the psychosis and that successful normalization of the responsiveness might be an effective therapeutic procedure—*Author's Summary*

KARNAKY, K J

The use of stilbestrol for the treatment of threatened and habitual abortion and prema-

ture labor: a preliminary report. *South M. J.* 35: 838. 1942.

Uterine pain of threatened, habitual, complete and incomplete abortion, and normal labor pains can be stopped immediately by giving 25 to 200 milligrams of stilbestrol in oil into the anterior wall of the cervix. Hard contracted uteri of abortions can be made to soften and assume normal consistency within 30 to 60 seconds, and will remain so for from 6 to 24 hours. Stilbestrol taken orally can be used to carry habitual abortion cases to term, and to stop labor pains and vaginal bleeding in cases of threatened and habitual abortion. Stilbestrol has caused no *in utero* deaths in 20 cases of normal pregnancy. Normal children have been born to 33 mothers who have received large doses of stilbestrol because of threatened, habitual abortion, or premature labor. Stilbestrol taken orally does not produce nausea in the pregnant woman, and, apparently, prevents morning sickness.—H.W.

KERMAN, E. F.

Testosterone therapy of involutional psychosis. *Arch. Neurol. & Psychiat.* 49: 306. 1943.

Twelve men were carefully selected as permitting an unequivocal diagnosis of involutional melancholia. They were observed for considerable periods to rule out the probability of spontaneous improvement. Courses of testosterone propionate in oil in dosage of 25 mg. were given twice weekly for thirteen weeks. After two months a second seven weeks' treatment was begun. In only a single instance did any significant degree of improvement occur.—R.G.H.

KING, J. K.

Roentgen therapy to the pituitary gland in functional disturbances of and associated with menstruation. *South M. J.* 35: 616. 1942.

This report is based on a study of 230 patients who were treated by roentgen irradiation of the pituitary gland for functional disorders of endocrine origin, manifested by disturbances of the menstrual cycle, headaches, nervousness, fatigue, subnormal sex life, sterility, low metabolic rate and abnormal weight. No hormonal assays on these patients are reported, and thyroid substance is the only hormonal therapy employed. Of 230 patients, ranging from 12 to 47 years, 105 were completely relieved, 61 were improved, 19 were not benefited and 45 were not followed. Excessive bleeding is most amenable to pituitary irradiation, while amenorrhea due to secondary

glandular dysfunction responds favorably in many cases. Irradiation can do nothing for hysteric menorrhea or dysmenorrhea unassociated with other symptoms, although if either are merely one feature of this syndrome correction may be expected in about 50% of the cases. Irradiation also has a beneficial effect on the fertility and life of the patient.—H.W.

KNIGHT, R. P.

Functional disturbances in the sexual life of a woman. *Bull. Menninger Clin.* 7: 25. 1943.

An instructive discussion of the sociological psychology, prophylaxis, mental hygiene and treatment of sexual anxiety and frigidity.—R.G.H.

LATIMER, J. K.

The action of testosterone propionate upon the kidneys of rats, dogs and men. *J. Urol.* 48: 77. 1942.

Treatment of rats and dogs with testosterone propionate produced a renotropic effect, which was a true increase in tissue solids, due to an increase in cytoplasm. Renal function in dogs, measured by inulin clearance and diodrast time, could be increased by testosterone propionate in proportion to the increase in renal tissue. In humans, the largest safe dose improved renal function only when combined with the compensatory hypertrophy following nephrectomy. From autopsy reports, the kidney weight/body weight ratio of 50 adult, sexually active, human males was significantly higher than that of 50 adult sexually active human females. One hundred infants showed no sex difference. Blood pressure showed no significant change under this treatment with testosterone propionate, in rats, dogs or humans.—H.W.

MCCUNE, D. J., H. H. MASON AND H. J. CLARKE.

Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome). Report of a case in which increased urinary organic acids were detected and identified, with a review of the literature. *Am. J. Dis. Child.* 65: 81. 1943.

In this 9 year old boy the chief features were (1) severe hypophosphatemic rickets, renal glycosuria, and extremely reduced serum bicarbonate; (2) moderate polyuria, albuminuria and cylindruria with normal nonprotein nitrogen and urea; (3) acid urine with huge amounts of uric acid and organic acids; (4) slightly reduced

serum sodium and fixed base, (5) excessive urinary phosphorus and calcium during a balance study, (6) normal sodium, chloride and magnesium metabolism, and (7) no obvious effect from 1,000 U.S.P. units of vitamin D daily for several weeks. Other therapeutic recommendations were of little value, the patient died, no autopsy was performed. The authors identified, for the first time, the organic acids: 82 per cent amino acids, 1 per cent lactic acid and 7 per cent beta-hydroxybutyric.

The data were interpreted to indicate diminished ability of the renal tubular epithelium to reabsorb dextrose, amino acids and phosphate from the glomerular filtrate. Inasmuch as the requirement of cation to neutralize the organic acids was still not satisfied by the production of a highly acid urine, of large amounts of ammonia and of increased urinary volume, mineral cations of the body fluids were called on, with resultant depletion of fixed base. Recurrent hypoglycemia was thought to be responsible for the excretion of beta-hydroxybutyric acid. The presence of lactic acid was ascribed hypothetically to either renal tubular or hepatic dyscrasia.

Thirty similar cases have been reported in the last 15 years. Hypophosphatemia was demonstrated in 17 of these, in 3 the serum phosphate was elevated, in 10 it was not determined. In 4 other instances excessive amounts of urinary organic acids have been recognized but not identified. Eleven autopsies have been made. Pathologic changes have been most consistently found in the kidney, with serious involvement of the tubular epithelium more often than of the glomeruli. In a few cases the liver has shown changes varying from focal necrosis to cirrhosis. Our cases (possibly another) showed deposits of crystalline cystine throughout the reticuloendothelial system. Cystinosis may have been overlooked in other cases.

The syndrome bears the name of Fanconi, who postulated in 1931 that the symptoms developed because of a hereditary inadequacy of the renal tubular epithelium which allowed dissipation of dextrose and cations. The authors believe that the additional data accumulated since then support the concept of a renal origin for the syndrome, but favor a defect in the tubular reabsorption of phosphorus rather than of cation. They consider this syndrome one phase or aspect of a larger morbid series which merges imperceptibly on one side with classic hyperphosphatemic renal rickets and on the other with the poorly understood, so called "cystine rickets"—*E C R, Jr*

MENNINGER, W. C.

The emotional factors in pregnancy. *Bull Menninger Clin* 7 15 1943

An attempt has been made to touch on the more important psychological stresses and strains associated with pregnancy and a few of the manifestations of these. The universality of pregnancy and its importance as one of the major experiences in the life of a woman, both psychologically and physiologically, justify an extensive study from the psychosomatic point of view. Such a study should encompass the attitudes of women, both married and unmarried, towards pregnancy in terms of their individual life experience and situation. Such a study should also include the close cooperation of the obstetrician and psychiatrist in the investigation and management of a large number of pregnant women through the entire course of the pregnancy. And finally, the study should include a close investigation of women during the post-partum state—the woman's struggles with herself and her husband and her baby. Such an approach should be extremely fruitful as a source of material which might be used to aid psychological and physiological adjustment to the reproductive process—*Author's Summary*

MENNINGER, K. A.

Emotional factors in organic gynecological conditions. *Bull Menninger Clin* 7 47 1943

It is suggested that emotional factors demand consideration even in those cases in which organic pathology is obvious. A case is presented in which there was evidence that emotional factors determined a fatal uterine hemorrhage. Possible mechanisms are discussed whereby connection can be traced between emotional factors and structural disorders such as hypotonicity of the pelvic muscles, leading to prolapse, asthenic dystocia and obstetrical laceration. The relation of emotional factors of possible significance to fibromyomata, endometritis and false pregnancy is briefly discussed—*R G H*

NIXON, W. C. W., MARGARET D. WRIGHT AND E. C. FIELLER

Vitamin B<sub>1</sub> in the urine and placenta in toxemia of pregnancy. *Brit Med J* 1 605 1942

Urine analyses and placental analyses were made for vitamin B<sub>1</sub> by the assay method in a series of 106 pregnant women among hospital populations. It was found that in cases of eclampsia the amount of vitamin B<sub>1</sub> excreted in the



urine on admission to hospital was significantly lower (0.94 I.U.) than in normal pregnancies (3.39 I.U.). The concentration of the vitamin was also lower in pregnancies accompanied by eclampsia (5.9 I.U.) than in normal pregnancies (19.4 I.U.).—*D.A.M.*

PEARLMAN, W. H., AND G. PINCUS.

The metabolism of estrone in men. *J. Biol. Chem.* 147: 379. 1943.

Massive doses of estrone, as the acetate, were injected into 7 young men. From the strong phenolic fraction of the urine collected for 96 hours following injection, there was recovered a small amount of crystalline estriol. An exogenous origin of the estriol isolated is precluded. The high concentration of estrogenic activity in the weakly acidic, phenolic, non-ketonic fraction is due chiefly to  $\alpha$ -estradiol. This is substantiated by the changes in the activity of this fraction after the application of mild oxidative procedures.—*Author's Summary.*

SHUTE, EVAN.

Vitamin E and premature labor. *Am. J. Obst. and Gynec.* 44: 271. 1942.

A series of 46 cases of threatened premature labor in the author's private practice were treated prophylactically with vitamin E in the form of wheat germ oil or ephynal. Sixty-seven per cent were taken to term with delivery of live children.—*E.C.H.*

SIMPSON, S. L.

The increasing importance of endocrinology in general medicine. *Brit. M. J.* 27: 247. 1943.

The author reviews the manifestations of endocrine diseases in various branches of medicine including surgery and gynecology. He concludes that an Endocrine Clinic should be an integral part of a hospital and should serve as a model for modern methods of investigation, research and therapy in disease.—*R.B.G.*

VICKERS, V. S., AND H. C. STUART.

Anthropometry in the pediatrician's office. Norms for selected body measurements based on studies of children of north European stock. *J. Pediat.* 22: 155. 1943.

The authors present 21 tables of normal values for body weight, head circumference, chest circumference, chest breadth, body length (recumbent and standing), pelvic breadth (recum-

bent and standing), crown-rump length, sitting height, and growth increments compiled from measurements they have made on Boston and girls between the ages of birth and 10 years. The values for each sex are based on data from 140 children at birth, and from progressively smaller groups at succeeding ages to 25 years. The medians and certain other percentiles of the extremes of the series, the means and standard deviations are given. Standard measurements and the techniques for obtaining them are defined.—*E.C.R., Jr.*

WETZEL, N. C.

Assessing the physical condition of children. Case demonstration of failing growth and termination of "Par" by the grid method. *Pediat.* 22: 82. 1943.

The author has devised a chart or "Grid" to appraise objectively the growth and development of children from the plotted record of their height and weight. The technique of appraisal involves the evaluation of physical status in terms of physique, developmental level and nutritional grade at every point, and the evaluation of physical progress from point to point. One case is reviewed in detail to illustrate the principle and the method of analysis.—*E.C.R., Jr.*

WETZEL, N. C.

Assessing the physical condition of children. II. Simple malnutrition: A problem of failing growth and development. *J. Pediat.* 22: 205. 1943.

The author applies his "Grid" to the problem of malnutrition and demonstrates how it can be utilized to detect conditions of failing growth and development and to evaluate their response to suitable therapy. One case is analyzed to illustrate the procedure.—*E.C.R., Jr.*

WRIGHT, C. A., AND E. H. WILLIAMS.

Endocrine therapy in dementia praecox. *J. Rec.* 156: 28. 1943.

Certain types of psychic abnormalities are accompanied by endocrine dysbalance. In the male homosexual the androgen-estrogen ratio increases, in the female it increases. In dementia praecox, there is a deficiency of the homogonadotropic hormone, without a rise in the heterogonadotropic hormone, as well as other endocrine deficiencies. Treatment with massive doses of the deficient hormones, as determined by assays, may help the mental abnormalities. Five illustrative cases

dementia praecox accompanied by endocrine deficiencies are given. Two females were treated with estrogens, one male with androgens, a hypopituitary male with androgen and gonadotropins, and a hypoadrenal male with adrenal cortex extract. In all cases cited, remission of the mental symptoms occurred.—*H.W.*

## GONADS

LYLA, E. P., AND A. F. HENDERSON.

Castration for carcinoma of the prostate: a report of the immediate results. *J. Urol.* 48: 673. 1942.

Forty patients with carcinoma of the prostate were castrated. All showed immediate general improvement, with relief of metastatic pain. In out of 26 patients there was an elevation of serum acid phosphatase, which dropped with castration or estrogen therapy. X-rays showed an increase of bone healing and disappearance of metastases. In 30 patients who returned for examination the prostate was markedly reduced in size. Stilbestrol is indicated in cases not responding satisfactorily to castration and to relieve hot flashes.—*H.W.*

WEBB, J. C., AND S. S. KETY.

Recent advances in testosterone therapy. *New England J. Med.* 228: 338. 1943.

The physiology, methods of administration and indications for testosterone therapy in diseases peculiar to the male, gynecologic conditions and in general diseases are reviewed. The authors conclude "There is as yet no evidence of permanent harm resulting from its moderate and clearly indicated usage."—*R.B.G.*

WICKERS, W.

The placenta: a modified arteriovenous fistula. *South M. J.* 35: 593. 1942.

The circulatory changes occurring in pregnant women, particularly the fall in the arteriovenous oxygen difference, the marked elevation in the venous pressure of the lower extremities, and the arteriovenous bruit heard over the placental site, can be explained by assuming that the placenta is an arteriovenous fistula. Studies of the venous pressures in both femoral veins and an arm vein, the appearance of edema, and, after delivery, the placental site, were made during pregnancy, and through delivery, on 23 patients. The highest femoral venous pressure recorded was that of 260

mm., in a case with central placenta previa. The pressures in the legs exceeded those of the arms in all females studied with a mean of 108 mm. In 12 of the patients with anterior or posterior placental sites the venous pressures in both legs were about equal, with equal swelling in both ankles. In 11 patients with lateral placental sites, the femoral venous pressure and the edema were greatest on the side of placental implantation. Blood shunted from the uterine artery to the uterine vein on the side of implantation would transmit an increased pressure to the femoral vein.—*H.W.*

BISCHOFF, F., AND G. J. CLARKE.

Influence of nephrectomy on ovarian response to gonadotropins. *Am. J. Physiol.* 138: 241. 1943.

Greater ovarian weights were produced in partially nephrectomized rats than in intact animals, by equivalent amounts of gonadotropins. Augmentation after sheep pituitary substance was of low magnitude and, after pregnant mare-serum hormone, may have been accounted for by loss of body weight following operation. The response to prolactin, however, was so greatly augmented in the nephrectomized rats (ovarian weight increase: 175 to 240% of that in the intact animals) that this result is regarded as significant. The author suggests that the normal refractoriness toward prolactin is a result of a low renal threshold for this hormone.—*J.W.E.*

CHUTE, R., A. T. WILLETS AND J. F. GENS.

Experiences in the treatment of carcinoma of the prostate with stilbestrol and with castration by the technique of intra-capsular orchidectomy. *J. Urol.* 48: 682. 1942.

Twenty-six of 27 cases of inoperable carcinoma of the prostate, treated by surgical castration, or a combination of surgical castration with stilbestrol therapy, showed rapid relief from pain of metastases, when present, great improvement in appetite and general health, and reduction in size and induration of the prostate with improvement in ability to urinate in most cases. Quickest and most satisfactory results were obtained by castration followed by the injection of 10 mg. of stilbestrol per day for 5 to 10 days. When stilbestrol alone is used, patients have to be kept on a maintenance dose of 1-3 mg. per day. No beneficial effect was noted on bony metastases. If elevated the acid phosphatase level fell towards normal after therapy, while the alkaline phosphatase usually rose. 17-ketosteroid determina-

tions were made in 18 cases before and after castration. In all but 4 cases the value fell immediately after castration. In these 4 cases the acid phosphatase decreased, and the patients did well clinically, while the 2 patients who did worst had values that fell after castration. The authors' impression is that the 17KS level does not give information of value as to the progress of disease in cases of carcinoma of the prostate. The technique of intra-capsular orchidectomy presented has certain cosmetic advantages in retaining a semi-normal appearance of the scrotum.—H.W.

DEAN, A. L., H. Q. WOODWARD AND G. H. TWOMBLY.

The endocrine treatment of cancers of the prostate. *J. Urol.* 49: 108. 1943.

Results of endocrine treatment of 60 patients for carcinoma of the prostate are presented. Thirty-four were surgically castrated and, in all but 2 cases, showed marked relief of symptoms. Eight treated with 2-5 mg. of stilbestrol daily showed improvement as great, though slower, as that obtained from orchidectomy. Stilbestrol is also beneficial when relapses occur following surgical castration. In 19 out of 26 patients the elevated serum acid phosphatase fell after castration to values slightly above normal, while 2 patients who showed no significant change had no clinical improvement after operation. Stilbestrol produced similar changes. Castration elevated the serum alkaline phosphatase in 12 of 26 patients, with marked increase in the degree of osteoplasia. Twenty-seven of 35 treated by bilateral orchidectomy showed mean preoperative levels of 16.6 mouse units of estrogen and 6.1 mg. of 17-ketosteroids per 72 hours. In all but one of these there was a post-operative drop of estrogen excretion to a mean of 8.5 mouse units. The 17KS output of 16 patients rose in 11 patients and fell in 5, after castration. Eleven of 16 patients on whom gonadotropic hormones were determined showed definite post-castration rises, while 5 had amounts too low to measure before or after operation. In 12 patients primarily treated with stilbestrol the 17KS excretion fell from a mean of 8.9 to 5.4 mg., while the estrogen excretion rose, presumably due to stilbestrol excretion. Castration apparently frees the anterior pituitary from testicular control, as shown by increased gonadotropic hormone excretion and increased adrenal stimulation, causing a rise in 17-ketosteroid output. Stilbestrol inhibits the anterior pituitary, causing a fall in the excretion of gonadotropin, and 17-ketosteroids. Both pro-

cedures cause marked clinical improvement, suggesting that the gonadotropic hormone from pituitary is not directly concerned.—H.W.

DIAZ, J. T.

Pseudohermaphroditism. *Am. J. Dis.* 65: 67. 1943.

The case is reported of a child, aged 7½, was angular in build; had long head hair; a nasal voice; normal breasts; no facial or axillary hair; pubic hair 3 to 5 cm. long, which had been present for 3 years; a phallus 3 cm. in length and 1.8 cm. in diameter, which was held down by a thin membrane extending from the fenulum to the base and attached to the midline of the perineum; an external urinary meatus at base of the phallus; no vaginal opening; structures resembling labia majora on each side of the perineum; absence of testes in the scrotum or in the inguinal canals; no prostate; an almond-sized mass on rectal examination which was thought to be a uterus. The child being brought up as a girl. The author considered the patient to be a cryptorchid male with hypospadias because chorionic gonadotropin (antuitrin S) 500 rat units intramuscularly twice weekly for 5 weeks caused an increase in the phallus to 4.1 cm. in length and to 2.4 cm. in diameter. The author postulated that in a male gonadotropin would stimulate the interstitial cells of the testes to produce androgen which in turn would cause an increase in the size of the phallus; in a female, gonadotropin would have no definite effect on the external genital structures. He proposed this biologic test with gonadotropin as an aid in determining the functional nature of the gonads of patients whose sex is apparent. No operation was performed.—E.C.R., Jr.

GILBERT, J. B.

Studies in malignant testis tumors. VIII. Malignant tumors in pseudohermaphroditism: review of sixty cases and a case report. *J. Urol.* 48: 1. 1943.

Sixty cases of pseudohermaphrodites with testicular tumors, and one additional report, are reviewed in this paper, comprising about 1 per cent of the testis tumors studied in detail. There were 38 unicellular tumors (seminoma); 14 teratomas, and 9 miscellaneous or "malignant" tumors. These tumors were located in the scrotum of the testis twice, in the inguinally retained testis 4 times, and in the abdominally retained testis 48 times. In 8 patients both gonads were involved. Fr-

one patients were considered primarily operable, 11 had operations performed in spite of metastases while 9 were considered inoperable. Four patients survived 5 years or more, 3 with unicellular tumors, and 1 with a teratoma. In the bilateral testis tumors there were 4 unicellular, 3 teratoma, and 1 adenoma. In the entire group, only 4 Aschheim-Zondek assays were performed, and these were found to be negative. No androgen or estrogen assays were made. The 52 non-involved gonads were located in the scrotum 3 times, in the perineum once, in the inguinum 8 times, and in the abdomen 38 times. Inguinal hernia was present in 12 patients; in some patients it may be the only lead to the identification of pseudohermaphroditism.—H.W.

HICKLL, G. P.

Pregnanediol excretion in normal women. *New York State J. Med.* 42: 2103. 1942.

Sodium pregnanediol glucuronide excretions (24 hour urines) were determined at weekly intervals during pregnancy in 5 women and during normal cycles in 3 women. Curves of excretion are similar to those reported by others. Variations of considerable magnitude were noted.—D.A.M.

JOHNSON, W. O.

Vaginal biopsy studies after total hysterectomy. *South M. J.* 36: 23. 1943.

Studies of vaginal biopsies, from 4 months to 5 years after total hysterectomy, are reported on 50 patients. There is evidence of continued estrogenic effect upon the vaginal mucous membrane up to 4 years after operation. Those patients who had lowered ovarian function at the time of operation had a more senile type of vaginal mucosa than the others in the group. Most marked changes occurred in two cases where radium had been used for cancer, and where castration had been performed prior to hysterectomy.—H.W.

LAPIN, J. H., W. KLEIN AND A. GOLDMAN.

Cryptorchidism. *J. Pediat.* 22: 175. 1943.

Thirty-nine of 200 boys treated at the Bronx Hospital have been followed since treatment for 2 to 9 years. Of these, 14 cases (35.9%) were at first considered to have responded successfully, but later this group was reduced to 6 cases (15.3%) by the omission of two patients in whom descent of the testes occurred without treatment, two patients in whom the descent was only partial, and four in whom hypogonadism ensued.

The failures are analyzed. Therapy consisted of varied amounts of chorionic gonadotropin; testosterone propionate and thyroid in addition were employed too infrequently to warrant analysis. From these cases and a review of the literature, the authors concluded: (1) treatment for cryptorchidism should not be instituted until the patient was 14 years old, but then was advisable to relieve the deficiency of androgenic hormone formation and of spermatogenetic activity, and the psychologic handicap; (2) a preliminary test with endocrine therapy should be made in every case (except those with ectopic testes complicated by a substantial hernia in whom operation was inevitable), with the understanding that if the test failed to produce descent, the patient would be operated without delay to avoid the damage that the high abdominal temperature can do to testes that have become partially developed by therapy; (3) for this test chorionic gonadotropin is the only medication free from theoretical objections, providing it is given in a dosage not exceeding a total of 6,000 international units divided into frequent small doses during 6 weeks; and (4) a similar 6-week course of chorionic gonadotropin should be given immediately after operation to induce further testicular development.—E.C.R., Jr.

LESSER, M. A.

Treatment of angina pectoris with testosterone propionate. *New England J. Med.* 228: 195. 1943.

Twenty-one men and one woman with angina pectoris were treated with testosterone propionate. The favorable results previously reported by the author (24 cases) were again obtained. Four patients were studied by means of exercise tolerance before and during the course of therapy to obtain quantitative measurements of their improvement. The amount of exercise before the development of an anginal attack was markedly increased under testosterone therapy and the severity of attacks was correspondingly diminished. Medication was administered in 25 mg. doses every second to fifth day for a total of 5 to 25 injections. An average of 28 days elapsed before quantitative improvement was noted and a period of 43 days before this improvement was marked. The duration of beneficial effects of testosterone propionate therapy varied with the individual. The shortest period of benefit was 2 months and the longest period of relief from anginal attacks was 18 months.—R.B.G.

MILLER, M. L., AND R. A. MOORE.

Variation in the daily urinary excretion of androgens in relation to benign hypertrophy of the prostate. *J. Urol.* 48: 544. 1942.

The capon comb growth assay was used to study the daily androgen excretion, for a period of 30 days, of 4 men in the 8th decade, 2 with benign hypertrophy of the prostate, 1 normal, and one with an atrophic prostate. No significant differences were found in the coefficients of variation of these patients.—*H.W.*

POLLOCK, W. F.

Histochemical studies of the interstitial cells of the testis. *Anat. Rec.* 84: 23. 1942.

Substances with chemical properties of the known active steroids of the testis were found in the interstitial cells of cats and other common laboratory mammals. No like substances were detectable in other parts of the testis. Thus histochemical data support physiological evidence that interstitial cells are the source of testicular androgen.—*J.W.E.*

PORTNOY, L.

The diagnosis and prognosis of male infertility; a study of 44 cases, with special reference to sperm morphology. *J. Urol.* 48: 735. 1942.

Forty-four males, with a history of barren marriage of 1 year or longer, are presented. In 16 of these the seminal fluid was normal in all respects. Successful conceptions occurred later in 7 of these cases, 3 following treatment of the female partner. In 14 cases of subfertility, with oligozoospermia associated with asthenozoospermia and defective morphology, and 14 cases of sterility, with complete azoospermia, or very marked oligozoospermia and defective morphology only 1 conception occurred subsequently. Twelve of these men were given treatment to improve spermatogenesis, with no significant improvement in the seminal fluid, and no success in establishing pregnancy. The prognosis of male infertility, with or without treatment, is quite poor. A detailed method of assaying male fertility is presented, with classifications and illustrations of sperm morphology.—*H.W.*

SCHONFIELD, W. A., AND G. W. BEEBE.

Normal growth and variation in the male genitalia from birth to maturity. *J. Urol.* 48: 759. 1942.

Measurements were made and reported on the

genitalia of 1500 normal white boys. Relax and stretched penis length and circumference were measured directly. Testicular volume was estimated by comparison with a series of models of known volume. A high correlation was found between stretched and erect penis length. Cumulative frequency curves and growth curves, by age, are given for all factors measured. Growth curves for length and circumference show some pre-pubescent growth, followed by a marked increase during pubescence. Testis volume shows no change until pubescence when a phenomenon of growth starts, somewhat earlier than that of the penis. Chronological age is an unreliable guide to genital development after age ten, but no better one can be suggested. Genital growth is a pubescence phenomenon, far outstripping measurements such as height and weight. The testicular volume changes so markedly with pubescence that it may be employed for determining its onset.—*H.W.*

TAYLOR, N., AND R. L. SCHAEFER.

Non-neoplastic hypergenitalism. An analysis of seventeen cases. *Psychosom. Med.* 5: 1. 1943.

A brief review of the literature includes an outline of the known causes of hypergenitalism and notes on theoretical considerations. Seventeen cases of non-neoplastic hypergenitalism are analyzed with respect to physical, psychological and social findings. A composite description of this endocrine type is presented. No treatment is suggested but understanding of the problem is essential for all who manage juveniles and adolescents.—*Author's Summary.*

BRONSTEIN, I. P., J. A. LUHAN AND W. NAVRELIS.

Sexual precocity associated with hyperplastic abnormality of the tuber cinereum: Report on a case. (Abstract). *Arch. Neurol. & Psychiatry* 48: 1022. 1942.

A girl 22 months of age exhibited vaginal bleeding, enlarged breasts and vulval hair. The possibility of involvement of the hypothalamic apparatus was entertained. Intracranial symptoms were not present. In pneumoencephalographic studies, visualization of the ventricles and cisterns revealed nothing abnormal. The child died of meningitis. A detailed postmortem examination was made. In the region of the tuber cinereum a globular, grayish white, glistening mass, about 4 mm. in diameter, was observed in the midline just in front of the mammillary

odies. The pineal body appeared normal. Histologic examination of the tumor showed that it resembled in structure the tuber cinereum, and the diagnosis of a hyperplastic malformation (hamartoma in the sense of Albrecht's definition) rather than of ganglioglioma or pseudoheterotopia. The pituitary presented relative hyperplasia of the eosinophils of the pars distalis. Except for these alterations, the endocrine system was normal to macroscopic and microscopic inspection. The relation of the mass to the sexual precocity is discussed. Various mechanisms that might be responsible for this phenomenon are postulated. —R.G.H.

FARQUES, R. J.

Hypophysis and pigmentation. *Neurobiologia* 5: 1. 1942.

Extensive pigmentary disturbances in 2 patients were attributed to dysfunction of the pituitary gland, in view of a singular genital anomaly in the one case and the fact that the anterior and posterior clinoid processes were joined by a bony ridge in the other. Therapeutic results are discussed.—*Author's Summary.*

McLAREN, H., AND M. McLEOD.

Diabetes insipidus in pregnancy. Case. *J. Obst. and Gynaec. Brit. Emp.* 49: 51. 1942.

Onset of diabetes insipidus occurred in the 4th week of pregnancy. Symptoms disappeared completely following premature delivery 2 weeks later. Edema, jaundice and post-partum hemorrhage occurred during the puerperium.—*D.A.M.*

ASQUALINI, R. Q., AND A. AVOGADRO.

The action of pitressin on thirst in diabetes insipidus. *Rev. Soc. argent. de Biol.* 18: 88. 1942.

Two patients with diabetes insipidus were deprived of water until intense thirst and anxiety developed. The craving disappeared 20 minutes after an injection of 5 units of pitressin. This indicates that the pitressin influences other tissues besides the kidneys perhaps the receptor center of thirst sensation.—*A.E.M.*

VAZQUEZ-LOPEZ, E.

Structures of the neurohypophysis with special reference to nerve endings. *Brain* 65: 1. 1942. *Abst. Arch. Neurol. & Psychiat.* 49: 283. 1943.

This investigation was made chiefly on frozen sections of the pituitary gland of the horse, some studies also being made on the ox, sheep, rabbit,

guinea pig and rat. Nerve fibers were stained by silver and gold impregnation methods, to assure differentiation of connective tissue, nerve fibers and neuroglial prolongations. Nerve fibers to the hypophysis arise in hypothalamic nuclei, pass through the eminentia media of the tuber cinereum and enter the stalk in thick, close-set bundles. As they enter the pars nervosa, they fan out and, toward the distal portion, form a dense network of fibers running in all directions. Many of these fibers end in the acellular perivascular spaces formed by the neuroglia around the blood vessels of the neurohypophysis where they form extensive arborizations, including various swellings, clubbings and menisci. This profusion of nerve-ending apparatus is rarely equaled elsewhere in the body. A second group of fibers enters the pars intermedia where it appears to come into direct contact with the epithelial cells of the region and to form expansions and other structures, suggesting that nerve fibers end among these cells. Actual pericellular plexuses were not observed. A third group of fibers, in the most distal portion of the gland, form a system of nerve bundles lying beneath the connective tissue capsule of the pars nervosa and end in relation to special meningeal corpuscles which lie embedded in the thick fibrous covering of the apical region. The nerve fibers and nerve endings innervating the meningeal corpuscles are similar morphologically to those ending in the perivascular networks. The meningeal corpuscles appear to have only a sensory function. Furthermore, the morphologic appearance of the nerve endings in the perivascular spaces suggests a close relationship to perivascular nerve endings of a sensory character present in other parts of the body. These facts indicate that the great mass of the neurohypophysis consists of sensory elements and that the main function of the organ must be that of a gigantic perivascular receptive apparatus. Vazquez-Lopez suggests that this sensory system may consist of chemoreceptors and pressoreceptors concerned with regulation of metabolic and hormonal functions. This regulation is mediated through the diencephalic centers in which the nerve fibers to the neurohypophysis originate.—*R.G.H.*

## PANCREAS

CRAMER, H. I.

The influence of menstruation on carbohydrate tolerance in diabetes mellitus. *Canad. M. A. J.* 47: 51. 1942.

The author points out that before the days of insulin other observers had noted diminution in carbohydrate tolerance associated with menstruation in diabetic patients. Even in non-diabetics sugar tolerance had been found impaired in the menstrual period. Cases are pointed out in which diabetic acidosis was precipitated when the patient was in the premenstrual or menstrual period. In reviewing the admissions to the Royal Victoria Hospital over a period of years, it was noted that 47.2% of the cases of acidosis without obvious infection or other precipitating causes showed that menstruation had occurred at or about the time acidosis developed. The author then examined 11 menstruating diabetic females and noted the blood sugar before, during and—in some instances—after the menstrual period. Most of the patients failed to show any noteworthy disturbance of the carbohydrate metabolism at the menstrual period although some did show prolonged alteration just before the menstrual period. He concluded that in some diabetics an impairment of carbohydrate tolerance occurs at the menstrual period and that it may be severe enough to precipitate diabetic acidosis. He also concluded that in the same patient this upset may take place in one cycle and not in another.—*J.E.H.*

FISCHER, A. E., AND A. L. FLORMAN.

Transitory hemiplegia associated with hypoglycemia in a diabetic child with congenital heart disease. *Am. J. Dis. Child.* 65: 73. 1943.

An 11 year old girl gave the following picture: (1) congenital heart disease with tetralogy of Fallot; (2) at 9 years, right hemiplegia due to cerebral thrombosis, with recovery after three months; (3) at 11 years, diabetes mellitus for which insulin was required; and (4) an insulin-induced hypoglycemic reaction with a second right hemiplegia, which disappeared when the blood sugar levels were restored to normal. The importance of recognizing similar insulin reactions is emphasized.—*E.C.R., Jr.*

GANEM, J. F.

Influence of folliculin on diabetes. *Rev. méd. de Rosario* 32: 599. 1942.

Estrone, in daily doses of 10,000 to 50,000 I.U., was given intramuscularly to 18 females with moderate diabetes, for periods of 10 to 15 days. There was no effect on glycosuria or hyperglycemia in 9, a decrease in either symptom or a slight decrease in both symptoms in 5, and

greatly decreased hyperglycemia and aglycuria in the remaining 4. The results were similar in pre- and post-menopausal subjects, although in one patient whose diabetes began at menopause the estrone therapy was successful; this considered as probably coincidental. Estrone indicated in therapy of diabetes in insulin-fractory females, and a technic of treatment presented. The only side-effect of estrone noted was insignificant uterine hemorrhage. Its mechanism of action in diabetes is probably through inhibition of the diabetogenic factor of the anterior pituitary.—*Courtesy Biol. Absts.*

GOLDFARB, W., AND M. GOLDEN.

Absorption of carbohydrates in humans. *Pr Soc. Exper. Biol. and Med.* 51: 134. 1942.

Blood sugar curves after oral ingestion of varying concentrations of glucose were determined. In 30 minutes increase in blood glucose was greater with 5% glucose than with 30% and in patients in insulin coma, recovery was more rapid with the lower concentrations. Intestinal absorption is influenced by relative intestinal and blood glucose concentrations.—*D.A.M.*

KAPLAN, A., C. ENTERMAN AND I. L. CHAIKOFF

Effects of insulin on the blood lipids of man. *Endocrinology* 32: 247. 1943.

Injection of massive doses of insulin into human subjects failed to alter significantly the blood lipid level. The concentration of free and esterified cholesterol, total fatty acids and phospholipids in the blood were unaffected by the most complete removal of glucose from the blood stream.—*H.O.H.*

MENKIN, VALY.

Gluconeogenesis and cellular injury. *Am. J. Physiol.* 138: 396. 1943.

An acute inflammation induced in dogs by intrapleural injection of turpentine is accompanied by a marked local gluconeogenesis due to increased proteolysis in the inflammatory area. The excess glucose formed diffuses into the circulation giving rise to hyperglycemia. The experiments support the view that excessive blood glucose levels in diabetics with superimposed infections is due to local protein catabolic processes with gluconeogenesis.—*D.A.M.*

STEINER, M. M., AND P. C. TRACY.

Diabetic coma, acute pancreatitis and bacillus welchii peritonitis. *Am. J. Dis. Child.* 65: 36. 1943.

The following series of events is thought to have occurred in a 13 year old white boy: (1) severe enteritis and duodenitis with changes in the pancreatic ducts; (2) entrance of bile or infected intestinal contents into the pancreas (3) activation of trypsinogen with extensive necrosis of the pancreas including the islet tissue; and (4) onset of fatal diabetic coma with abdominal pain and vomiting, during life thought to be due to the "abdominal syndrome" seen in uncomplicated diabetes, but at post-mortem proven to be due to acute pancreatitis and *B. welchii* peritonitis. This was the only instance of these complications in 10 autopsied children who had died of diabetic coma at the Children's Memorial Hospital of Chicago from 1921 to 1942.—*C.R., Jr.*

FLA, O.

Hexamine-insulin; a clinical study. *Rev. méd. de Rosario* 32: 956. 1942.

Hexamine-insulin, prepared by the addition of methenamine (urotropin) to insulin, has an immediate intense effect and a delayed action lasting for 12 hours. Its effects were tested on rabbits, nondiabetic and diabetic patients. In tests on 15 diabetics, comparison was made with protamine-zinc-insulin, and 7 case reports are given in detail. A chronology of insulin compounds and mixtures introduced to obtain long duration of hypoglycemic action is included. Hexamine-insulin is considered satisfactory for control of different grades of diabetes.—*Courtesy Biol. Absts.*

## PARATHYROID

ERNER, A. D.

Hyperparathyroidism with metastatic deposits in the kidneys, *South M. J.* 35: 671. 1942.

A case is reported of a parathyroid tumor in a 45-year-old woman. The hyperparathyroidism caused by this tumor, which was demonstrated at autopsy, caused marked decalcification of the bones, with metastatic deposits of calcium in the kidneys and their pelvises.—*H.W.*

## THYMUS

JRN BULL, F.

Removal of malignant thymoma in a case of myasthenia gravis. *Arch. Neurol. & Psychiat.* 938. 1942.

A case of myasthenia gravis associated with malignant thymoma is reported. Successful removal of the thymic tumor did not result in any improvement of the myasthenia gravis, as has been reported in some other cases.—*R.G.H.*

## THYROID

BARTLETT, W.

Essential biochemical derangements in hyperthyroidism. *Arch. Surg.* 45: 103. 1942.

In hyperthyroidism even with severe increase in symptoms the alkaline reserve of patients remains normal if patients are kept at rest. However, with excretion, the CO<sub>2</sub>-combining power of plasma decreases. With improvement of the hyperthyroid state during treatment prior to operation, urinary total acids, organic acids and NH<sub>3</sub> fall and the pH increases. After thyroidectomy, plasma alkaline reserve increases.—*D.A.M.*

DENKER, P. G., AND R. L. OSBORNE.

Aberrant thyroid tumor of the vertebrae with compression of the spinal cord. Recovery after operation and high voltage roentgen therapy. *Arch. Neurol. & Psychiat.* 49: 277. 1943.

A tumor which had involved and partially destroyed the spinous process and laminae of two segments of the thoracic vertebrae of a 27-year-old man was partly removed by surgical operation. It was found to consist of normal thyroid tissue. It was further treated with high-voltage roentgen rays. Follow-up observations after 10 years revealed complete recovery. Review of the literature failed to disclose any similar case of benign metastatic thyroid lesion of the spine with complete recovery.—*R.G.H.*

FOHIERINGHAM, W. TEJERINA.

Recurrent hyperthyroidism. Postoperative persistence or relapse. *Rev. méd. de Rosario* 32: 819. 1942.

The etiology is discussed and 4 case reports are cited. Three had persistent hyperthyroidism after sub-total thyroidectomy, and 1 relapsed. Two of the 3 were cured by re-operation. The patient who relapsed following the first thyroidectomy was again operated, but so recently that the permanence of cure cannot be judged. Results at the Lahey Clinic showed 92% of 306 patients with recurrent hyperthyroidism presented symptoms of hyperthyroidism after re-operation.—*Courtesy Biol. Absts.*



FOURNIER, J. C. M., AND J. M. CERVINO.

Congenital myxedema without mental disturbance. *Arch. urug. de med., cir. y especialid* 20: 93. 1942.

The authors discuss an unusual case of congenital myxedema. The symptoms probably became obvious during the third year. At the age of 10, thyroid treatment was begun. The singularity of this case was the fact that although the usual physical disturbances and retardations had taken place, the mental age was normal.—*Courtesy Biol. Absts.*

KOBACKER, J. L.

Production of goiter and myxedema by thiocyanates. *Ohio State M. J.* 38: 541. 1942.

Treatment for hypertension of a 48-year-old woman, who previously had a moderate diffuse thyroid fullness, with potassium thiocyanate for a period of 17 months, led to myxedematous goiter with a B.M.R. of  $-30$ . Omission of thio-

cyanate and thyroid therapy brought about return to a normal state in 2 months. KCNS therapy a year later induced a mild degree of myxedema.—*D.A.M.*

STEWART, H. J. AND W. F. EVANS.

Periferal blood flow in myxedema. *Arch. Int. Med.* 69: 808. 1942.

Periferal blood flow in 6 patients with myxedema decreased in proportion to the reduction in B.M.R. Following thyroid therapy, periferal blood flow and cardiac output increased with improvement in clinical conditions.—*D.A.M.*

TROTTER, W. R., AND N. WALLACE.

Thyroxine in myxedema. *Brit. M. J.* 1: 183. 1942.

A patient who could not tolerate oral thyroid because of vomiting was treated satisfactorily with intravenous thyroxine, 7.5 mg. every 4 weeks.—*D.A.M.*



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## Excretion of Sex Hormones in Abnormalities of Puberty<sup>1,2,3</sup>

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THE INTERNAL SECRETIONS in childhood influence growth, metamorphosis and metabolic reactions. Growth rate and certain aspects of metabolism are easily studied. A different situation exists in regard to abnormalities of metamorphosis from childhood to adult life since they are not often recognized until the time when the normal changes should occur. Technics by which these processes may be more thoroughly studied have recently become available. Foremost among these is the determination of the sex hormones in the urine. In the last 6 years we have determined the levels of sex hormone excretion in children for valuation as an index of future metamorphosis as well as for an index of abnormalities in development which had already become manifest.

The information derived may thus be correlated with other data concerning these abnormalities.

There are very few data on sex hormone excretion in abnormalities of childhood. This is because normal standards had not been established through childhood and puberty, and it is only by means of the standard values determined in one's own laboratory that comparison of abnormal excretion rates can well be judged. The available material in this field has been summarized elsewhere (1).

### METHODS

The methods of analyses for estrogens, 17-ketosteroids and pituitary gonadotropins have been reported (1) and only a brief summary is given here. Assays were made on complete 24-hour collections of urine.

*Pituitary gonadotropic hormone.* Pituitary gonadotropic hormone was precipitated from the urine with 95 per cent ethyl alcohol, using essentially the original technic of Aschheim and Zondek. Assay was performed on inbred, immature, female mice (Bar Harbor C<sub>57</sub>) between 19 and 21 days of age and weighing between 6 and 8 gm. The urine was usually concentrated so as to permit detection of a minimum of 20 mouse units for the 24-hour specimen. One mouse unit (m.u.) is defined as the minimal amount of extract which, when injected in five aliquots over a period of 48 hours, will produce vaginal opening 96 hours after the first injection. Although the criterion of vaginal opening

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<sup>1</sup> The normal controls in this paper were established in collaboration with a Growth Study, funds for which were given to Harvard University by the Rockefeller Foundation.

<sup>2</sup> Reported at American College of Physicians and at the Association of American Physicians (*Trans. Ass. Am. Physicians* 55: 306, 1940). Additional data have been accumulated since then and are incorporated in this paper.

<sup>3</sup> This is reprint No. 573 of the Cancer Commission of Harvard University.

for determining gonadotropic activity is probably not as specific as others, such as follicle stimulation or an increase in ovarian or uterine weight, it is adequate to detect significant variations from the normal.

*Estrogens and 17-ketosteroids.* The urinary estrogens and 17-ketosteroids were extracted with benzol by the method of Smith and Smith (2). An aliquot of the benzol extract was then used for assay of the total estrogens. No attempt was made to separate the estrogens into their various components since the quantity of material available was much too small for such studies. The estrogens were assayed on inbred mice (Bar Harbor C<sub>57</sub>) or rats (Slonaker strain) with a modification of the Allen-Doisy method. The 17-ketosteroids in the remaining extract were separated from the estrogens, using in principle the method of Gallagher, *et al.*, (3). Values are expressed in international unit equivalents of estrone.<sup>4</sup> The technic of assay was that described by Oesting (4) modified for the photoelectric colorimeter (5). Conditions such as temperature, light and purity of reagent were kept as uniform as possible. Values are expressed as milligrams equivalent of crystalline androsterone.<sup>5</sup>

In view of the rapid strides in the development of technics of assay and in the chemical identification of the various hormones, standard methods should be available so that the actual values obtained in each laboratory can be compared with each other. Unfortunately, however, normal values of different investigators differ and therefore cannot always be directly compared. Consequently, the individual laboratory must at present depend upon its own set of standard figures for comparison with those obtained in disease. This has been done in the group of cases presented here by adhering to the original technics as much as possible because a proportion of our data for both normal and abnormal cases has been accumulated over the past 6 years and hence before the advent

of new information and possibly better methods of estimation.<sup>6</sup>

## RESULTS

*Normal controls.* The data on 104 normal control children have been reported in detail elsewhere (1). There is a steady but slight increase in 17-ketosteroids and estrogen excretion in both sexes from the ages of 6 to 10 years. After 10 the excretion level of 17-ketosteroids rises more abruptly in boys, as does the estrogen excretion in girls. However, there is also a consistent increasing level of excretion of 17-ketosteroids in girls and of estrogens in boys. Approximately 1.5 years before the menarche, a cycle of estrogen excretion which gradually increases in amount develops in girls. During this period and thereafter it is necessary to determine the estrogen excretion repeatedly. This has not been possible in some of the abnormal girls in our present series, so that the excretion levels can only be compared with minimal or maximal rates. A cycle of 17-ketosteroid excretion was found in either sex nor any cycle of estrogen excretion in boys. Variations in the 17-ketosteroid excretion occur from day to day, but these are seldom greater and usually less than 25 per cent of the mean of a series of consecutive daily assays. Consequently, several determinations on carefully collected urine specimens are usually adequate. The same may be said for estrogen excretion in the male.

Tests for the presence of pituitary gonadotropic hormone in the urine with the technics described are usually negative in normal girls before the age of 11 and in normal boys before the age of 13. Such a negative response does not imply that gonadotropic function is lacking before these ages. The steady increase in the excretion levels of the estrogens and of the 17-ketosteroids in the younger age groups suggests such an activity. Therefore a negative response merely means that the method is inadequate to detect very small amounts of the hormone in the urine, even though it may be present. A positive response prior to these ages and elevated levels thereafter may be considered a

<sup>4</sup> The crystalline estrone (Theelin) was supplied for standardization through the courtesy of Dr. E. A. Sharp of Parke, Davis & Co., Detroit, Mich.

<sup>5</sup> The crystalline androsterone which was used as a reference standard was generously supplied by Dr. Erwin Schwenk of the Schering Corp., Bloomfield, N. J., and by Dr. Ernst Oppenheimer of the Ciba Pharmaceutical Products, Inc., Summit, N. J.

<sup>6</sup> In the past two years parallel assays of the urinary 17-ketosteroids were carried out using several accepted technics described in reference 5. Although the titers of the same specimen varied with the different methods, the trends in excretion rates were identical.

dicative of unusual pituitary activity or of a limited gonadal response. Assays for the pituitary gonadotropins were not made in every case.

### *Abnormal Cases*

In the term abnormal puberty is included all degrees of variation from average growth and development, although many of these children may eventually become normal adults. On the basis of the standards derived from the present study (1) an impression can be formed of the relative levels of excretion of the sex hormones in children whose development is atypical. The rates of excretion in both normal and abnormal children of the same chronologic age have been arranged in tables.

The children included in this study, so far as we know, have only functional endocrinopathies. Observations on children with functioning tumors have been reported elsewhere (6). Functioning tumors of endocrine origin give rise to striking increases in the rate of sex hormone excretion while in the cases described here the variations from the normal range are not so dramatic. This indicates that marked increases in hormone excretion may be due to hyperfunctioning tumors, while slight to moderate increases are more suggestive of functional abnormalities or of benign hyperplasias of the endocrine organs. One example of this was in a 2-year-old child with a hyperfunctional abnormality of the pituitary gland with true *pubertas praecox*, which was shown at autopsy to be due to stimulation from a non-malignant tumor arising in the hypothalamus. The hormone excretion levels were similar to those of a normal young adult and not the very high levels found in true hyperfunctioning tumors.

*Precocious puberty.* This is a manifestation of an early stimulus to normal sexual growth and development representing an abnormally early adolescence. This is frequently but not necessarily accompanied by precocious somatic development as well. There were 8 children in this group (table 1), all but two of whom were very advanced in sexual development. Cases 2 and 8 were apparently normal children, 11 years old, but who were slightly advanced in development. This observation was in accord with the

sex hormone excretion rates which were in the normal range for children about 13 years of age. These children therefore appeared to represent a physiological variation of normal puberty which is more a matter of time of onset than of form. The other 6 children represent cases of far greater abnormalities for they demonstrated sex and somatic changes at very early ages. Gonadotropic assays were performed for 6 of these 8 children and 5 had elevated excretion levels on one or more occasions. At these ages such findings are usually indicative of pituitary overactivity and are comparable to the values for normal children at or near puberty. In 7 of the cases there was an elevation of the excretion level of both estrogens and 17-ketosteroids. In case 7 there was an elevation of urinary estrogen only. She was a tall girl who was menstruating and had developed secondary sex characteristics. The estrogen excretion levels in this person differed little from those of case 6, but the latter also had an elevated 17-ketosteroid excretion, and, interestingly enough, had not menstruated.

*Retarded puberty and growth.* In the 14 cases of retarded puberty the reduced level of the estrogen and 17-ketosteroid excretion parallels the degree of physical retardation (table 2). For example, case 19, was a girl, 14 years old, who was considerably retarded in sexual metamorphosis. The excretion level of the 17-ketosteroids was normal, but there was a definite reduction in estrogen excretion. By contrast, case 16 was very retarded, both physically and sexually. The excretion values for both estrogens and 17-ketosteroids were approximately those of an 8-year-old girl. Ten months after the first assays there was an elevated titer of pituitary gonadotropin. In case 22 growth was very slow and the signs indicative of puberty had not appeared. The excretion level of estrogens was not unusually low, but the 17-ketosteroid values were subnormal when she was first studied. Two years later, at the age of 17, this girl still had not arrived at the menarche, but there was a rapid development of the secondary sex characteristics and an increase of 3 inches in height. It is to be noted that at this later time the 17-ketosteroid and the gonadotropin excretions were normal for a girl at puberty. Case 16 (see above) differed from case 22 primarily in the

TABLE 1. HORMONE EXCRETION STUDIES IN 8 CASES OF PRECOCIOUS DEVELOPMENT

Pt.	Age, yr., mo.	Bone Age, yr.	Wt., lb.	Ht., in.	Estrogens i. u. 24 hr.	17-Ks mg./24 hr.	Gonadotropin M.U./24 hr.	Clinical Remarks	Normal Values for Chronological Age		
									Estrogen i.u.	17-Ks mg	Gon. troy M
Male patients											
1 <sup>5</sup>	4—3	7.5	61.5	43.0	43.0	3.5	>120	Muscles large; genitals, testes, prostate enlarged. At age 5-6 bone age 11-3; ht. 47.5 in.; wt. 60 lb.; genitals further advanced, voice low; normal sugar tol., blood cholesterol 101 mg. %	6.0 (4-9)	3.2 (2.4-4.8)	<
2 <sup>1</sup>	11—1	13.5	90.0		84.0 40.0	17.4 14.4	>120 <80	Slightly advanced development	30.0 (10-60)	11.0 (8.5-13.0)	<
Female patients											
3 <sup>2</sup>	4—0	7	46.5	42.0	296.0 130.0	8.6 9.2	>40 >36	Continued development; breasts and uterus enlarged; no menses	8.0 (5-10)	2.5 (1.5-3.6)	<
4 <sup>2,4</sup>	4—1 4—4	8	64.0	49.8	160.0 96.0	4.0 5.4	ND <40	Breasts enlarged. Progressive development; B.M.R.—+19%			
5 <sup>2</sup>	5—5	10	42.0	48.5	154.0 89.0 32.0 28.0 48.0 45.0	6.5 5.5 7.5 7.7 7.2 6.8	>87 <22 <37 <26 >60 <20	Progressive development; pubic hair developed 6-6. Breasts enlarged; vaginal bleeding at 6-8, wt. 47.3, ht. 50.3. B.M.R.—5%	8.0 (5-10) 9.0 (5-15)	3.0 (1.8-3.6) 3.0 (2.0-4.2)	< <
6 <sup>2,4</sup>	7—1  7—5 8—2	12	75.2	53.0	176.0 80.0 112.0 64.0 130.0 96.0 84.0	11.1 10.6 12.1 9.0 8.4 10.4 14.9	ND <30 <30 ND <30 <36 <30	Moderately progressive development. Breasts enlarged	20.0 (5-35)  20.0 (10-35)	4.2 (3.0-6.0)  4.9 (3.6-7.5)	<  <
7 <sup>2,4</sup>	7—1 7—1 7—2 7—6	7	68.0	55.0	136.0 112.0 168.0 119.0	6.0 5.9 6.3 5.0	>28 <28 <28 >18	Progressive development; breasts enlarged, vaginal bleeding. Blood cholesterol 154 mg. %, B.M.R.—19%			
8 <sup>3</sup>	11—2	14-15	131.2		150.0 125.0 125.0	12.0 8.4 9.7 10.8 9.2	ND	Short and stocky, slightly advanced adolescence with menses at 10-11. Blood sugar, 70 mg. %. Blood cholesterol 84 mg. %	76.0 (25-150)	9.6 (6.0-10.8)	±

<sup>1</sup> Hair on upper lip in addition to pubic hair. <sup>2</sup> Body configuration feminine, advanced for age. <sup>3</sup> Also axillary hair.

<sup>4</sup> Vaginal epithelium cornified. <sup>5</sup> Average of five determinations.

ND—not determined. Pubic hair was present in every case. Figures in parentheses represent range of normal values per 24 hours.

relatively low estrogen excretion. The advent of pubertal changes in *case 16* was signified by the excretion rate of gonadotropic hormone as evidenced by the subsequent sexual development with the onset of menstruation two years later. This is analogous to observations reported by us (1) in normal children at an earlier age in whom the first excretion of detectable amounts of gonadotropic hormone generally accompanied the onset of striking pubertal metamorphosis.

The care to be exercised in the interpretation of findings during the period of puberty is demonstrated by *case 20*, a girl, who was 14 years and 8 months of age at the time of study and who showed no development of secondary sex characteristics. The urine of this girl was collected twice a week over a period of 4 weeks. If only the first 5 samples had been assayed for estrogens the cyclic excretion of these would have been overlooked. However, the last de-

terminations in this series showed that there was a cyclical output of estrogens. The excretion rate of the 17-ketosteroids was at the lowest limits of normal. Three months later breast development began and the first of subsequently normal menstrual cycles appeared just a year later. She grew 3.5 inches during this year. Therefore, was a girl with a completely neutropubertal configuration in whom prognosis of a normal development could be made because of the cyclical nature of estrogen excretion. The sex hormone excretion of this child of 14 years and 8 months corresponded with the usual estrogen excretion cycles of normal 11 or 12-year-old girls and the subsequent course was similar to that found in more normal female subjects.

In the males with retarded puberty at growth there were similar findings. Thus *case 11*, who was growing slowly but who otherwise was normal, had hormone excretion values that

TABLE 2 HORMONE EXCRETION STUDIES IN 14 CASES OF RETARDED GROWTH AND SEXUAL DEVELOPMENT

Age, yr, mo	Bone Age, yr	Wt, lb	Ht, in	Estro- gens 1 U / 24 hr	17 Ks mg /24 hr	Gonado- tropin mU /24 hr	Clinical Remarks	Normal Values for Chronological Age		
								Estrogens 1 U	17 Ks mg	Gonado- tropin mU
Male patients										
12-1 12-1 12-2 13-2 <sup>2</sup> 14-1	6	51.2	45.7	54 30 42 48 18	3.9 5.4 4.2 5.6 5.6	<40 <40 ND >66 ND	Short and stocky, genitalia infantile No body hair Very slow development even on intensive hormonal therapy, B M R -19%	30.0 (10-60)	13.0 (9.0-15.0)	±20
12-8 <sup>1</sup> 13-3 <sup>1</sup>	12	84.0	58.5	22 19	5.1 6.0	<20 <20	Early masculine configuration slight pubic hair Beginning to grow but small for age, B M R +6%	40.0 (20-80)	15.0 (10.0-19.0)	±20
14-4	13	81.5	61.5	28	9.4	<40	Normal configuration, genitalia slightly retarded and sl pubic hair, B M R -11%			
14-6 14-9 14-10 15-6	13	78.7	60	10 15 72 57	4.0 4.9 9.0 9.1	<20 <26 ND >100	Neuter configuration genitalia infantile no pubic hair B M R ±0%			
15-4	11-12	80.0	58.9	30	6.8	ND	Neuter configuration genitalia infantile no pubic hair B M R +14%			
15-5 16-9 17-4 18-9 <sup>1</sup> 18-11 19-4	10	63.0	54.5	260 320 192 184 50 280	ND 2.7 3.6 4.5 6.0 6.8	<40 ND ND >21 >45 >20	Neuter configuration genitalia infantile no pubic hair B M R +4%			
18-3 19-1	14	94.7	52.4	35 28	7.5 9.3	>80 >48	Short and fat, genitalia infantile No body hair B M R -2%			
Female patients										
12-1 13-10	Slightly retarded	61.5	51	32 20	6.8 6.0	<80 >108	No pubic hair no breast development until 13 yr 5 mo First menses at 14 yr 1 mo B M R +19%	240.0 (30-400)	9.6 (6.0-13.0)	±20
12-9 13-1	Slightly retarded	61.5	49.7	14 15	5.2 4.8	<20 <20	Neuter configuration body hair very sparse, genitalia infantile, no breast development B M R +37% Grew after testosterone therapy			
13-1 13-1 13-9	Normal	51.0	49.1	6 8 8	3.7 4.1 3.6	<20 <20 <20	" " "	300.0 (40-500)	9.6 (6.0-13.0)	±20
14-0	Slightly retarded	82.2	56.6	56	8.6	ND	Feminine configuration sl pubic hair genitalia infantile no breast develop- ment Progressive improvement at 14 yr 7 mo with development of labia and breasts and increased hair, B M R -4%	380.0 (50-600)	11.4 (9.0-15.0)	>20
14-7 15-0 15-6	Slightly retarded	80.0	55.7	10 20 24 30 24 270 432 144 30 450	8.0 7.2 8.4 7.6 8.7 8.1 7.8 8.4 7.2 9.0	ND	Neuter configuration, body hair sparse, genitalia infantile no breast develop- ment Marked improvement develop- ment of secondary sex characteristics and first menses at 15 yr 8 months B M R +20%			
15-1 15-3	Slightly retarded	63.0	52	30 14	6.2 4.5	<20 <15	Early feminine configuration, no body hair, genitalia infantile slight develop- ment of right breast B M R -9%			
15-0 17-0	Retarded	79.5	59	75 80	4.0 15.0	<30 >60	" "			

Receiving thyroid <sup>2</sup> On APL therapy <sup>3</sup> Average 8 determinations <sup>4</sup> Average 5 determinations <sup>5</sup> On testosterone therapy  
D—Not determined Blood sugar in each case within normal limits

normal in ratio and only slightly low in  
unt. Case 13 was very much retarded both  
ally and physically and the excretion levels  
very low for both estrogens and 17-ketoste-  
s On the contrary, the last two determina-  
s in case 12 showed a sudden rise in pitui-

tary gonadotropins, estrogens and 17-ketoste-  
roids This change occurred during the summer  
when he also developed sexually to a consider-  
able extent. We considered this as the begin-  
ning of puberty and advised against therapy, he  
was sent away to school, and

TABLE 3. HORMONE EXCRETION STUDIES IN 9 CASES OF ADIPOSE-GENITAL DYSTROPHY

Pt.	Age, yr., mo.	Wt., lb.	Ht., in.	Estro- gens I.U./ 24 hr.	17-Ks mg./ 24 hr.	Gonado- tropin M.U./ 24 hr.	Clinical Remarks	Normal Values for Chronological Age		
								Av. Est. & Range I.U.	Av. 17-Ks & Range mg.	Gona- trop. M.U.
Male Patients										
23 <sup>1</sup>	10 - 4	130.5	60.5	28.0	7.2	<60	Improved with thyroid and dietary therapy; B.M.R.—24%	22.0 (10-15)	9.4 (7.5-13.0)	<2
24	11 - 0	159	59.5	24.0 16.0	4.5 5.2	<20 <20	Had treatment for undescended testicles 2 mo. before observation. B.M.R.+34% (?)	30.0 (10-60)	11.0 (8.5-13.0)	<2
25	11 - 2	160	58.2	18.0	5.1	<80	Blood cholesterol 148 mg.%; normal sugar tolerance; improved with thyroid and dietary therapy; B.M.R.—9%			
26 <sup>2</sup>	11 - 4 12 - 2 12 - 4 12 - 11 13 - 3	130.2	59.2	24.0 18.0 36.0 15.0 72.0	7.2 5.6 5.2 6.5 10.9	<80 ND ND <40 >34	Flat sugar tolerance curve; slight improvement with thyroid and dietary therapy; marked improvement with pregnant mare's serum; B.M.R.—22%	30.0 (10-60)	13.0 (9.0-15.0)	±2
27	11 - 5 13 - 6	83.5	51.0	40.0 45.0	7.0 8.4	ND <40	Blood sugar, 95 mg.%; improved with thyroid and dietary therapy; rapid metamorphosis at 15 yr. 3 mo.; B.M.R.—17%			
28	13 - 8	175	61.5	16.0 29.0	11.6 11.0	<20 <26	Normal sugar tolerance curve; marked improvement on regimen of thyroid, diet and pregnant mare's serum; B.M.R.—20%	40.0 (20-80)	15.0 (10.0-19.0)	±2
29	15 - 2 15 - 8	108.2	56.4	90.0 128.0	10.9 16.0	<20 <50	Seen first at age 7; some improvement with diet and thyroid, but still abnormal at present; B.M.R.—17%			
30 <sup>3</sup>	16 - 0	179	66.1	75.0 105.0	7.5 7.5	<20 <20	Had treatment for undescended testicles 2 months before observation; B.M.R.—15%			
Female Patients										
31	14 - 9	151	66.0	45.0	8.4	ND	Improved with diet and thyroid, but was beginning to show metamorphosis when first seen. B.M.R.—12%	380.0 (50-600)	11.4 (9.0-15.0)	>2

<sup>1</sup> Bone age advanced.<sup>2</sup> Thyroid extract continued throughout. Pregnancy urine extract, 7700 u. for 4.5 months between first and second determination. Pregnant mare's serum, 4500 u. for 6 weeks between fourth and fifth determination.<sup>3</sup> Bone age, 14 yr.

Roentgen of sella turcica normal in all cases; bone age normal except as indicated; body hair absent or sparse in all except 31. The genitalia were infantile in all cases.

no growth in the subsequent 4 months. However when he returned home after 8 months he had developed sexually, had grown 3 inches in height and had gained 13 pounds in weight. It is, therefore, clear that this sudden rise in hormone excretion levels not only paralleled a physical change but also presaged a continued development.

The boys in this group who had the most

marked growth retardation showed the most profound abnormality in the rate of sex hormone excretion. This was particularly true in case 14, age 19, who remains dwarfed and infantile although he has received endocrine treatment for the last 11 years including almost every type of pituitary growth and gonadotropic preparation which has been made available. In this patient the excretion of estrogens was

very high and of 17-ketosteroids very low, the latter at levels about normal for 4 years of age. In spite of the high estrogen excretion rate the body configuration was neuter. The testicles were like those of a completely immature child. Testosterone therapy which was commenced at 18 years and 9 months of age produced a striking change for about 6 months. The urinary estrogens decreased, the 17-ketosteroids increased, and, for the first time, the urine gave evidence of pituitary gonadotropic activity. Clinically, he seemed to be advancing not only sexually but with a definite increase in bone age. With the cessation of improvement, the urinary estrogen levels rose again, although the gonadotropic and 17-ketosteroid excretion remained unaltered. We are unable to explain the elevated estrogen levels, which are unusual in our experience for this type of case.

*Adiposo-genital dystrophy* is a frequent deviation from normal puberty. It is associated with marked obesity of the torso, infantile genitalia and gonads which are often undescended in the male. These characteristics often disappear spontaneously leading to a normal pubertal metamorphosis. It is to be distinguished from the obesity found in many vigorous children with rapid growth and sexual development and from the rare Frölich's syndrome which is characterized by delayed osseous development and growth, a flat blood-sugar curve, a somewhat low basal metabolism and a tumor of the pituitary gland. Determination of sex hormone excretion levels in cases of adiposo-genital dystrophy usually shows either low normal or moderately lowered 17-ketosteroid excretion with normal or slightly elevated estrogen excretion. This additional evidence for the identity of this syndrome may explain the feminine configuration and delayed sexual development encountered in the disease.

Case 26, age 11 years, 4 months, when first seen was clinically typical of marked adiposo-genital dystrophy with one undescended testicle which, on good authority retracted after an attack of chicken pox at 6 years of age. For 4.5 months between the first and second urinary determinations this patient was given gonadotropic therapy,<sup>7</sup> without any obvious effects.

He was then given pregnant mare's serum,<sup>8</sup> for 6 weeks between the fourth and fifth urinary determinations. During these 6 weeks the physical development of the boy was remarkable. The descended testicle doubled in size, and the undescended testicle, although not large, could be felt high up in the scrotum. Hair developed over the mons, the body configuration became more masculine and he grew 1.7 inches, gaining only 2 pounds in weight. This great change in the physical configuration was accompanied by an increased excretion rate of 17-ketosteroids. The excretion level of gonadotropins became elevated, but this was to be expected since the determination was made while the boy was receiving pregnant mare's serum.

#### DISCUSSION

The value of studying the urinary excretion of the gonadotropic and sex hormones in endocrine abnormalities is clear since they may be of considerable aid in the diagnosis of the etiology and course, as well as in the prognosis of the response to treatment. Evidence exists that the urinary 17-ketosteroids and estrogens represent excretory products of steroids produced both by the gonads and the adrenal glands (7, 8, 9). This information is of considerable value in the interpretation of the data on the excretion of these hormones. It should be emphasized that in some of the cases reported here the deviation from the normal range is so slight that the excretion levels may possibly be considered normal. This pertains, primarily, to those patients who clinically were considered as cases representing borderline variations of normal puberty. In contrast the hormone excretion levels in the grossly abnormal patients are sufficiently out of the average range to warrant the supposition that they are definitely atypical. Similar trends of hormone excretion levels are found in analogous clinical abnormalities. The interpretations, therefore, are based largely on the accumulated data rather than on the individual case.

*Precocious puberty.* In general, in precocious puberty not caused by neoplasms, there is a moderate elevation in the urinary excretion of the gonadotropins, estrogens and 17-ketosteroids which approach levels characteristic for

<sup>7</sup> Pregnancy urine extract (Antuitrin S) 7700 units, Parke Davis & Co.

<sup>8</sup> Anterior-pituitary-like hormone (Anteron) 4500 units, Schering Corp.



adults. These levels are essentially the same as those for older children, with whom the degree of skeletal, somatic and sexual metamorphosis of the precocious child runs parallel. Occasionally, the excretion level for one of the hormones may be normal, but in our experience none has been found to be below normal in this type of patient. Assay for the sex hormones are of value in differentiating precocious puberty from similar syndromes produced by neoplasms or hyperplasia of endocrine organs. In the latter abnormalities, particularly those of the adrenal glands or gonads, the hormone excretion levels are usually very high. Furthermore, except when the primary lesion stimulates pituitary secretion, it is unusual to find elevated excretion levels of each of the hormones. For example, tumors of the adrenal cortex, especially carcinoma, give rise to a marked elevation of excretion of the 17-ketosteroids and estrogens, particularly the former, whereas the granulosa cell tumor of the ovary is usually associated with a marked increase in the excretion of estrogens alone, without apparent change in the 17-ketosteroids. An increase in pituitary gonadotropins would be unusual with either type of tumor. Intracranial neoplasms producing pubertas praecox offer the greatest difficulty in differential diagnosis from those syndromes in which no definite etiologic factor can be ascertained. As far as we can tell hormone excretion rates in this type of neoplasm are only slightly higher or may easily fall into the range of the cases reported in this section. Moreover, there is usually an elevation of the excretion levels of the pituitary gonadotropins, 17-ketosteroids, and estrogens because the primary stimulation is probably of the anterior pituitary gland. Therefore, the clinical syndrome of precocious puberty, coupled with a knowledge of the sex hormone excretion rates, should aid materially in a diagnosis of the site and nature of the primary lesion.

*Retarded growth and development.* In contrast to precocious puberty, these syndromes may be due to hypofunction of the anterior pituitary or of the gonads, or of both organs. Hypofunction of the anterior pituitary gland usually results in decreased excretion levels of gonadotropic hormones, estrogens and 17-ketosteroids. However, failure to recover urinary gonado-

tropins implies, but does not necessarily prove pituitary hypofunction since our present methods may not be adequate to recover small amounts. On the other hand, primary gonadal deficiency in the presence of normal gonadotropic function may give rise to an elevation in the excretion of the gonadotropins. Depending upon the sex of the individual, the excretion rates of the estrogens or 17-ketosteroids are depressed. This may be explained by the concept that the gonadotropic hormones stimulate only the gonads and have no apparent direct effect upon the adrenals. Cases of individuals having primary ovarian insufficiency associated with *decreased stature and high urinary gonadotropin* titers have been reported previously (10, 11). In this present series, a male, *case 15*, may fall into the category of primary gonadal hypofunction. Thus, it seems that the variations in excretion rates of the various hormones may depend upon which of the glands is primarily deficient in function. Primary pituitary hypofunction may be differentiated from end organ deficiencies in some instances by the injection of potent gonadotropic extracts (*case 26*). Subsequent to such therapy, an increase from low levels of 17-ketosteroid excretion in the male and of estrogen excretion in the female may indicate an ability of the gonads to respond to proper stimulus and the failure of the pituitary gland to provide such a stimulus. Failure to respond to the stimulus may signify gonadal deficiency with or without hypofunction of the pituitary.

*Adiposo-genital dystrophy.* It is commonly held that this syndrome may occur as a result of dysfunction of the pituitary gland. The level of sex hormone excretion in this study confirms this point of view. Pituitary gonadotropic hormone was not recovered in any untreated patient. The 17-ketosteroid levels were usually below average in the male, but about normal in the female. The estrogens, however, were normal or slightly above normal in every male, but in the one female, *case 31*, the excretion was considerably below the average range for her age and sex. This suggests that the gonadotropic function of the anterior pituitary was decreased thus resulting in a diminished excretion of the urinary 17-ketosteroids in the male and the estrogens in the female. Since there is evidence

that the adrenals produce substances which are excreted in the urine as estrogens and 17-ketosteroids it seems reasonable to postulate in view of the retarded sexual development that the excretion levels of the hormones in these cases represent largely the secretion of the adrenal glands rather than the gonads. However, this does not imply that there is an inability of the gonads to respond to a proper stimulus for in case 26 the injection of gonadotropic hormone was followed by a significant rise in 17-ketosteroid excretion. Adiposo-genital dystrophy seems to differ primarily from cases with retarded growth and puberty of pituitary origin, in the degree of somatic development. Thus, each syndrome may represent a different type of pituitary dysfunction. This seems to be borne out clinically since in the case of retarded growth and puberty there is a delay in skeletal and gonadal development, whereas in adiposo-genital dystrophy there is a deficiency in the gonadal development with an associated obesity.

*Relationship of bone age, bone or somatic growth, chronologic age and the excretion of the sex hormones.* Conclusions with regard to growth rate are dependent upon the accuracy of normal standards. We have used as standards the most recent figures of Stuart (12) for children up to 72 months, and those of Meredith (13) and Boynton (14) for the older child. A careful distinction must be made between bone age and bone growth for the former is an indication of the development, metamorphosis and maturation of bones, whereas the latter merely implies an increase in length and diameter. Therefore, they should be considered separately since some of our observations indicate that bone age and bone growth may be dependent upon different factors. Our previous study has demonstrated that the levels of excretion of 17-ketosteroids in normal children are usually correlated more closely with the physical and skeletal development than with chronologic age (1). This is confirmed in these children in whom physical development and maturation deviate widely from the normal. The estrogen excretion level may also parallel physical development but here is not such a close association. In the female child the estrogen excretion levels correlate more closely with the degree of sexual development. An interesting example of this is

furnished by case 7 in whom the 17-ketosteroid levels correspond to the bone age and chronologic age whereas the estrogen levels, which were elevated, paralleled the rapid sexual development and somatic growth. A further study of these correlations may further differentiate the factors concerned with these various aspects of growth.

*Sexual metamorphosis.* It was discussed in another paper (1) that the higher estrogen excretion in the female and the higher 17-ketosteroid excretion in the male were probably due to the addition of the respective gonadal secretions to that of the adrenals. Since these hormones are probably responsible for and their excretion parallels the sexual metamorphosis in the normal child, these levels would be expected to correspond to the sexual age in the precocious or retarded child. The data confirm this viewpoint.

*Estrogen—17-ketosteroid ratio.* It is apparent that the excretion of estrogens, 17-ketosteroids and perhaps the gonadotropins, is correlated with the abnormalities of growth and development. The chief difficulty in the interpretation of these data lies in the lack of knowledge of the relationship of the estrogens to the 17-ketosteroids, for there are some cases in which the excretion levels of these two sex hormones are not equally distorted from the normal. Normal children of either sex at any given age show a rather constant relationship between the urinary levels of the hormones. Before the age of 9 there is little difference in either sex, but after this time the relationship changes in that the excretion levels of estrogens become progressively higher in girls and those of the 17-ketosteroids in boys (1). Alterations or exaggerations of this ratio are striking in certain types of tumors of the gonads or the adrenals, but in the cases reported here, with but few exceptions, the relationship remains constant regardless of the levels of the excretion. For example, in *pubertas praecox* not only the levels but the ratio correspond to that of an older normal child with whom the degree of development compares. Deviations from this ratio are found in the adiposo-genital syndrome in the male, in which there is a relatively lower level of the 17-ketosteroid excreted and, if any change, a somewhat elevated

estrogen excretion so that the ratio approaches that of the female. This is extremely interesting inasmuch as the body configuration also tends toward the feminine type. Such change in ratio appears to be of considerable importance in evaluating the physiologic response to these hormones. The evidence is too great to be ignored that in many respects the estrogens and androgens are antagonistic in their action both in animals and in man. Abnormal ratios, in our experience, have been associated with similar clinical deviations. It also appears obvious that the amount of hormone necessary to produce changes in the body is much smaller in early life than in the adult or senescent individual. This indicates a greater susceptibility in the growing organs to such a stimulus. The young organs respond to even a mild stimulation, while senescent organs behave as though they had become immune.

*Possible etiologic factors in the production of these syndromes.* The production of the above syndromes has been ascribed to a number of etiologic factors. The acute exanthemata with a possible accompanying encephalitis have been listed as the more common causes, but developmental defects such as internal hydrocephalus and malformations within the brain have also been reported. In a surprisingly large number of our patients there was a history of onset following exanthemata, particularly scarlet fever and mumps, although there was no good evidence that there was an accompanying encephalitis.

#### SUMMARY

Children were studied because they showed deviations from the normal rate of growth and sexual development. Analysis of urinary excretion rates of pituitary gonadotropins, estrogens, and 17-ketosteroids indicates that these rates are correlated with the extent of metamorphosis rather than with the chronologic age of the child.

The importance of these relationships and their use in the differential diagnosis and prognosis, and as an aid to treatment is discussed.

We are indebted to Miss Lois E. Towne and Miss J. Kelley for technical assistance; to the Children's Hospital of Boston for the privilege of studying four of their patients, cases 1, 2, 8, and 23; to Dr. R. Wagner for case 9, and Dr. G. J. Rubin for case 5.

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#### ADDENDA

Since this paper was submitted for publication, an article on the 17-ketosteroid excretion in normal and abnormal children has appeared: Talbot, N. B., A. M. Butler, R. Berman, P. M. Rodriguez and E. A. MacLachlan. *Am. Dis. of Child.* 65: 364, 1943. The interesting monograph, "Somatic and Endocrine Studies of Puberal and Adolescent Boys," has also just been received by Greulich, W. I., R. I. Dorfman, H. S. Catchpole, C. I. Solomon and C. Culotta. Vol. VII, Ser. No. 33, No. 3. Monographs of the Society for Research in Child Development—National Research Council, Washington, D. C., 1942. Both of these investigations are in essential agreement with the work presented here.



# Gonadotropin Excretion in Normal Men and Women and Cases of Hysterectomy, Menopause, Migraine, Epilepsy and Eunuchoidism

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THERE HAS NOW accumulated considerable evidence concerning the urinary gonadotropin excretion of human females and males. The following study, although not offering many new data, may serve to corroborate accepted results, especially since a somewhat different technic from that often employed has been used.

## METHOD

The technic of concentration is modified from that of Frank (1) and involves acidification to pH 5 and precipitation with 4 volumes of alcohol of the first morning specimen, dialysis of the precipitate through cellophane for from 4 to 6 hours in the cold (or more recently, washing with 80% alcohol), and 9 injections (two daily) of the entire amount into a 21-day-old female rat. As an end point, the uterine weight is recorded. However, when this increases above 120 g., the ovaries are also usually weighed, since the uterine weight soon reaches a plateau beyond which it cannot increase.

Although most of the curves shown were made from data obtained by procedures in which the technic of dialysis was utilized, lately we have, instead, washed the precipitate twice with 200 cc. of 80 per cent alcohol in water in order to remove the toxic salts. Sodium and potassium salts are much more soluble in 80 than in 95 per cent alcohol. This washing is followed by another 200 cc. of 95 per cent alcohol and then by ether. More recently Varney and Koch (2) have shown that alcohol as dilute as 50 per

cent may be used to diminish toxicity without loss of gonadotropic activity.

The rats are fed a stock diet without added NaCl, a separate supply of salt being available in the cage. Although we believe that it is the K salts which are most toxic (3) the animals undoubtedly tend to show some effect from the NaCl content of the injected solutions.

## RESULTS

Figure 1 represents the gonadotropin excretion

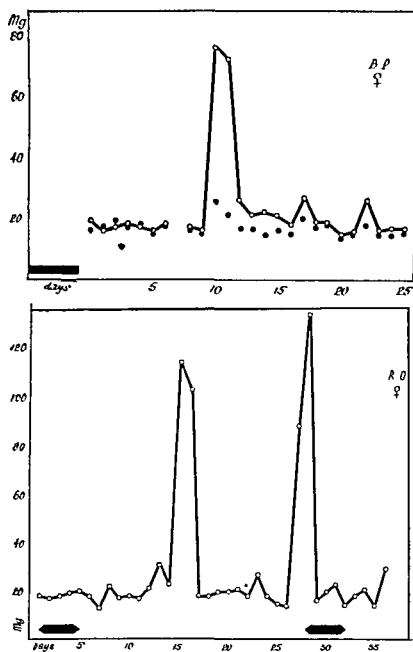


FIG 1 (upper). Gonadotropin excretion in normal female; solid line, rat uterine weight; black circles, rat ovarian weight; horizontal bars, menses.

FIG. 2 (lower). Gonadotropin excretion in normal female; uterine weight in 21-day-old-rat.

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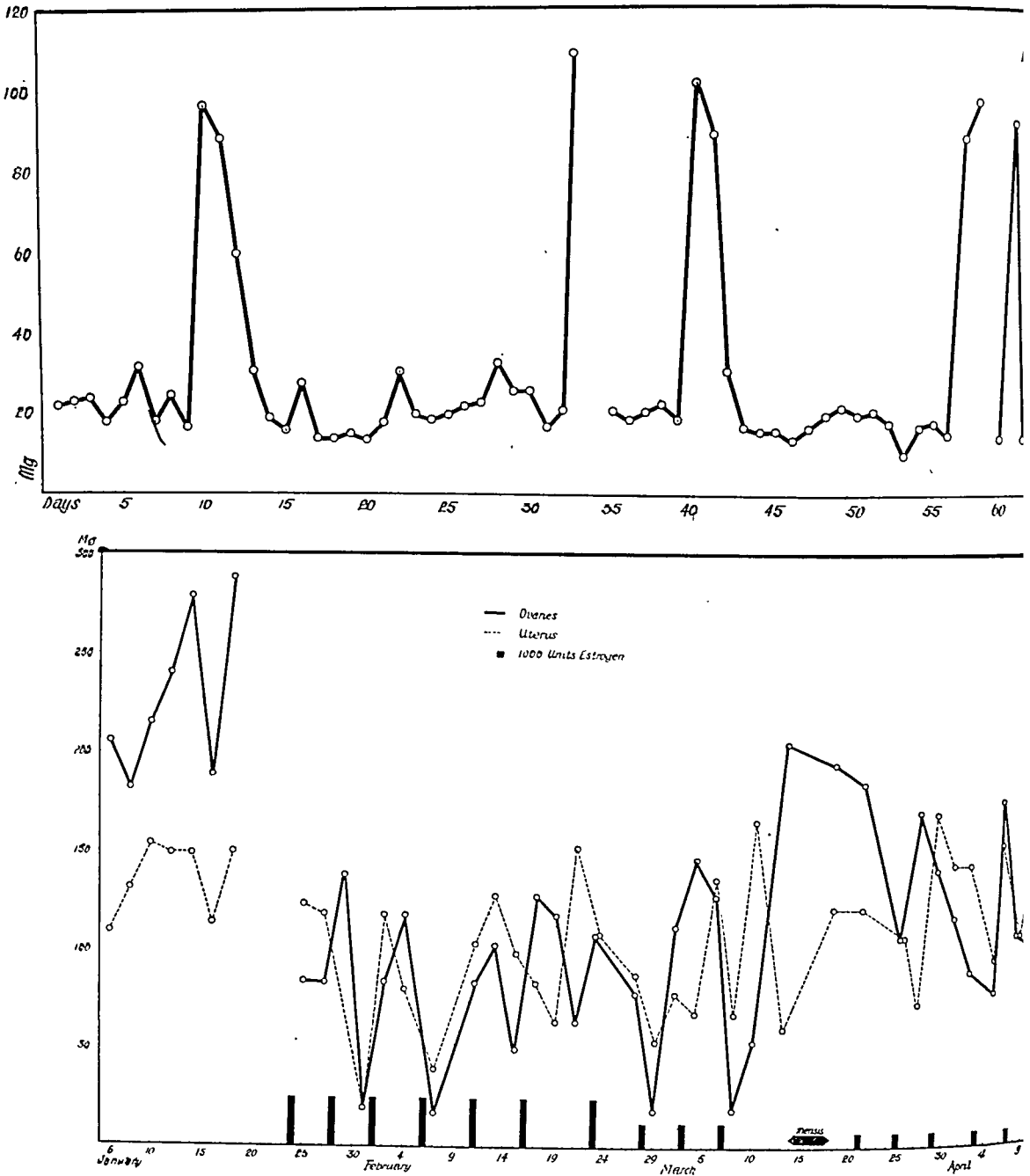


FIG. 3 (upper). Gonadotropin excretion in hysterectomized female; uterine weight in 21-day-old rat.

FIG. 4 (lower). Gonadotropin excretion in female with premature menopause. Reduction of amount of hormone excretion following estradiol benzoate, 10,000 R.U. per injection for 7 injections; less inhibition by 3 doses of 5000 bleeding following temporary cessation of therapy with rise in excretion of gonadotropin; less inhibition with 5 injections of estradiol benzoate of 3000 R.U. each. Solid line, rat ovarian weight; broken line, rat uterine weight; upright bars, estrogen injections; horizontal bar, bleeding.

tion of a normal married female, 25 years old, and the curve corresponds to the single peaks obtained by this same technic in two other normal women (4, 5).

Figure 2 is the curve of gonadotropin excretion in a normal unmarried woman 24 years old. This is the first time we have obtained two peaks of gonadotropin excretion in a normal unmarried woman as reported by others.

Since no gonadotropin had been detected in the urine of a patient with congenital absence of the uterus and pseudo dysmenorrhea (1), it was suggested that absence of the uterus might have been concerned, the curve in FIG. 3 was plotted from data obtained on a married woman, 37 years of age, who had complete hysterectomy 2 years previously. Gonadotropin was present, being of the mu-

peak type as reported by Heller (7). This would indicate that the congenital absence of the uterus in our previous case probably was not associated with the lack of detectable amounts of gonadotropin hormone.

Figure 4 is that from data on a married nullipara in her twenties who had not menstruated since she was 18. The excessive amounts of urinary gonadotropin indicate a premature menopause. The rat uteri often reached the plateau of maximal hypertrophy of about 150 mg.; the ovaries, in the earlier part of the study at times weighed as much as 300 mg. Following intramuscular injection of estradiol benzoate (10,000 R.U.) about every 4 days, the excretion of gonadotropin dropped markedly, the greatest effect occurring apparently several days after injection. This may be due to the time required for absorption and consequent delay in inhibition of the pituitary, or to the fact that the body fluids contain so much of the gonadotropic hormone that some time is required for its excretion. A painful mastitis was produced with this dosage of estrogen, which was then reduced to 5000 R.U. for 3 doses. Temporary cessation of treatment resulted in the first menses in

years. Treatment was resumed at a dosage of 3000 R.U. which plainly produced less inhibition of gonadotropin excretion. Approximately the same dosage orally (1000 R.U. daily) of estradiol (not shown in the curve) produced even less

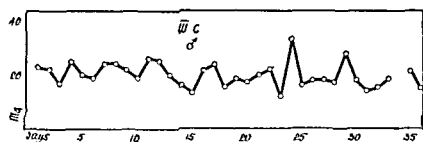


FIG 5 Gonadotropin excretion in normal male, uterine weight in 21-day-old rat.

effect. This would suggest that this method might be useful to compare the relative efficacy of various estrogens given orally and parenterally. Our results agree with the generally accepted statement that an estrogen dosage, which is adequate to afford clinical relief, is usually far from enough to inhibit markedly gonadotropin excretion.

Figure 5 is that obtained in the case of a normal male aged 25 years, and figure 6 is from the data on gonadotropin excretion of a male,

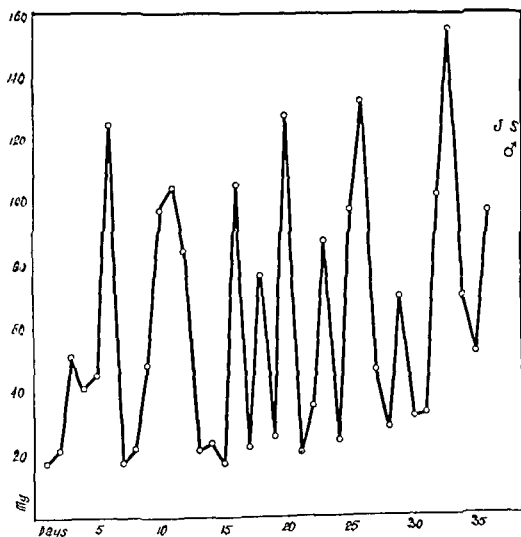


FIG 6 Gonadotropin excretion in male with migraine, uterine weight in 21-day-old rat.

24 years old, who suffered from attacks of migraine, averaging one a week. Not realizing at at the time the relationship between migraine and urinary gonadotropin (8), no record was kept of the frequency of the migraine. Following dietary treatment as suggested by Foldes (9), the patient has had no further attacks for over a year, and does not excrete measurable quantities of gonadotropin. Moreover, the marked diuresis usually following the migraine has also disappeared. This hormone excretion should be kept in mind when using gonadotropin excretion as an index of testicular tumors in the male and also might explain the irregular excretion of gonadotropin reported in some females. Migraine was not a factor in the high level and irregular excretion rate of gonadotropin of a female being treated for hypothyroidism (10) who has since become pregnant in spite of the abnormal gonadotropin excretion.

Because of the aphorism that *migraine is epilepsy of the autonomic system, and epilepsy is migraine of the cerebral cortex*, the gonadotropin excretion of a 42-year-old male epileptic showing degeneration was studied for 10 successive days. Large amounts of gonadotropin were found, the uterine weights being consistently over 100 mg., reaching a maximum of 150 mg. The ovarian weights were 50 mg. and above, reaching a maximum of 115 mg. However, two other young male epileptics who were having occasional convulsions were studied over a period of 20 days each, without finding any distinct amount of hormone, the uterine weights only occasionally reaching a maximum of 35 mg. All 3 patients were receiving phenytoin therapy.

A 40-year-old male with all of the characteristics of eunuchoidism excreted no appreciable amounts of gonadotropin over a period of 10 days. His medical history was not clear; an operation had been performed at an early age, which may have been castration, or an un-

successful attempt to remedy cryptorchidism. Lack of hormone in this case would indicate primary pituitary failure.

#### SUMMARY

A normal young woman had a single peak urinary gonadotropin between menses, and another young woman, two peaks. A hysterectomized woman had normal single and double peaks in corresponding periods. A young woman with premature menopause has a constant high urinary titer of gonadotropin, which was reduced in proportion to the dosage of estrogen suggesting a means of estrogen assay in the human female. A normal male had no appreciable excretion of gonadotropin; one with migraine showed a high and irregular level of excretion which disappeared with successful dietary treatment. One epileptic male excreted large amounts of gonadotropin but two others excreted none. A eunuchoid male did not excrete any demonstrable amount of gonadotropin.

We are indebted to Drs. Nathan Bloom, L. X. Kolipins, S. G. Page, and P. H. Drewry for their co-operation and assistance; to Dr. William Rhea Bond of Schering Corporation, Bloomfield, N. J., for the supply of estrogen; and to J. H. E. Stoeckel for assistance.

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# Metabolic Changes in a Patient with Addison's Disease following the Onset of Diabetes Mellitus<sup>1</sup>

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THE DEVELOPMENT of diabetes mellitus in a patient with pre-existing Addison's disease has been reported only once (1).<sup>2</sup> There are, however, 11 well-documented instances in which diabetes mellitus and Addison's disease have developed simultaneously or in which the onset of diabetes mellitus has antedated the onset of Addison's disease. In 4 of the 11 patients, Addison's disease and diabetes mellitus appeared to develop simultaneously (table 1). In the remaining 7 instances the onset of Addison's disease appeared

to follow the development of diabetes mellitus (table 2).

The case reported by Arnett in 1927 (2) has been referred to (11) as the first substantiated instance of the co-existence of the two diseases. A survey of the literature, however, revealed a case report by Unverricht in 1926 in which Addison's disease developed in a known diabetic (7). The case described by Crook and Russell in 1935 (13) had been reported in 1932 by Levy-Simpson (3) and hence these reports represent a single instance of the co-existence of the two diseases. Allen in 1930 (14) stated that only two patients with both diseases were encountered among 115 cases of Addison's disease and 3000 diabetic patients seen at the Mayo Clinic. No details were given in this paper, but it is to be presumed that the two cases referred to were those subsequently reported by Rowntree and Snell in 1931 (8, 9) in their monograph on Addison's disease. Mention might also be made at this time of a report by Brookfield and Corbett (15) concerning a diabetic patient who was observed at post-mortem examination to have bilateral adrenal atrophy and fibrosis. Blood pressure determinations were not recorded and abnormal pigmentation was not noted. This patient was admitted to hospital in severe diabetic coma and died 12 days later. Umber (16) reported the cases of 2 elderly diabetic patients who later developed what was thought to be Addison's disease. Neither of these two patients displayed any evidence of decreased insulin tolerance. The data presented are meager, and insufficient to warrant the inclusion of these two patients among the well-established cases of diabetes mellitus and Addison's disease.

Of the 7 patients with well-established diabetes mellitus, 5 showed a definite decrease in the severity of the diabetes following the onset of symptoms of Addison's disease. It is well known experimentally (17, 18, 19) that re-

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<sup>1</sup> This study was aided in part by a grant from the Committee on Research in Endocrinology, National Research Council.

<sup>2</sup> This patient was a 32-year-old housewife who, at the time of onset of diabetes mellitus in June, 1940, had manifested the classical signs of Addison's disease for more than one year. During this period she had been maintained in good condition on 5 mg. of desoxycorticosterone acetate injected intramuscularly 3 times weekly. The onset of diabetes occurred rapidly and was marked by polydipsia, polyuria and weight loss. At the time of onset of diabetes mellitus, the patient was 565 lbs. and 5'6" tall.

did well on regular insulin, and the maintenance dose subsequently fell to 28-40 units daily. In August, 1940, nineteen weeks after the onset of diabetes, she received an overdose of insulin while at home. She was brought to the hospital in a severe hypoglycemic reaction and despite the administration of intravenous glucose and adrenalin she expired. The etiology of diabetes mellitus in this patient was presumed to be familial. In the diagram the members of her family with diabetes are indicated with solid circles, whereas the non-diabetic members are indicated by open circles.

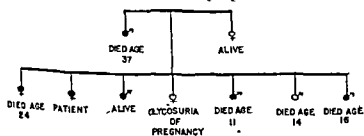




TABLE 1. PATIENTS WITH SIMULTANEOUS ONSET OF DIABETES MELLITUS AND ADDISON'S DISEASE

Author	Patient's Age	Sex	Duration of Diseases, Years	Pathological Findings Adrenal Glands	Insulin Requirement
Arnett (2) (1927)	39	F	3	atrophy	20-50 units daily
Levy-Simpson (3) (1932)	16	M	1	atrophy	10 units resulted in hypoglycemia
Gowen (4) (1932)	54	F	1.5	atrophy	5 units resulted in hypoglycemia (diabetes controlled by diet)
Koeppf and Bowen (5) (unpublished)	20	M	2	atrophy	no insulin (diabetes controlled by diet)

TABLE 2. PATIENTS WITH DIABETES MELLITUS WHO SUBSEQUENTLY DEVELOPED ADDISON'S DISEASE

Author	Patient's Age	Sex	Duration of Diabetes at Time Addison's Disease Developed, years	Apparent Etiology of Addison's Disease	Duration of Addison's Disease	Daily Insulin Requirements, units Prior to Onset of Addison's Disease	After Onset of Addison's Disease
Unverricht (6) (1926)	32	M	6	tuberculosis	2-4 months	40	5
Rowntree-Snell (7) (1931)	25	M	1	atrophy	15 months	0	20-30
Rowntree-Snell (8) (1931)		M	6	atrophy	18 months		
Rogoff (9) (1936)	25	M	4	denervation of adrenals	12 months	48-60	5-10
Bloomfield (10) (1939)	30	M	1	atrophy	(patient alive)	40	8
Bowen, <i>et al.</i> (11) (1942)	76	F	10	tuberculosis	12 months	0	improved glucose tolerance test
McCullagh (12) (1942)		M	7	atrophy	(patient alive)	40-120	40-50

removal of the adrenals modifies the course of diabetes in pancreatectomized or phlorhizinized animals.

The onset of diabetes mellitus in a patient with Addison's disease who had been intensively studied and who had received adrenal cortical hormone therapy over a period of 4 years prior to the development of diabetes provided a unique opportunity to investigate in man the nature of the modifying effect which these two diseases are thought to exert on each other.

PROTOCOL

J.H.H., (Johns Hopkins Hospital No. 160819, Peter Bent Brigham Hospital No. 62915), a 23-year-old white male, was admitted to the Johns Hopkins Hospital on Jan. 30, 1939, complaining of weakness, loss of appetite and discoloration of the skin. The present illness had begun during the winter of 1938 when the patient (then 22 years of age) first noted slowly increasing weakness. In May, 1938, headache and marked anorexia developed rather abruptly. At the same time generalized darkening of the skin became manifest. The patient was found to have a persistent

low-grade fever and subsequently developed general glandular enlargement. He was admitted to a hospital where a diagnosis of Addison's disease was made. The typical blood picture of infectious mononucleosis was observed and the heterophile antigen agglutination were found to be positive in dilutions of 1:64. The administration of large quantities of sodium chloride and adrenal cortical extract resulted in considerable improvement. He remained in fair health except for an acute attack of serum sickness in August, 1938, following an injection of tetanus antitoxin, when his temperature rose to 105°F. and he became comatose and went into shock. Following the administration of intravenous sodium chloride and glucose solutions and large amounts of adrenal cortical extract he made rapid recovery.

The family history and the patient's past history were noncontributory. There was no familial history of diabetes mellitus.

Physical examination on admission Jan. 30, 1939 revealed a thin, but well-developed, rather tired young man, not acutely ill. The temperature was 98.6°F. pulse 84 per minute, respiratory rate 18 per minute and blood pressure 92/50 mm. Hg. He weighed 63 kg. (139 lb.). The skin was deeply tanned over the entire body with numerous black freckles over the back. Some bluish mottling was present along the gum

gins. The thyroid was not remarkable and the ph nodes were not enlarged. The lungs were clear examination of the heart revealed no abnormality except a blowing systolic murmur at the apex. The and spleen were not palpable. The remainder of physical examination was not remarkable.

The laboratory findings were as follows: Hb. 93 per cent; red blood cells, 4.5 millions; packed red blood volume (hematocrit), 41 per cent; white blood cells, 9700; polymorphonuclears, 47 per cent; lymphocytes, 43 per cent; monocytes, 9 per cent; and eosinophils, 1 per cent. There were numerous abnormal phocytes resembling those seen in infectious mononucleosis. The blood Wassermann reaction was negative. The following blood chemical determinations were noted at this time: plasma sodium, 126.7 m.eq.; chloride, 95.2 m.eq.; and potassium, 8.2 m.eq. per 100 cc.; blood nonprotein nitrogen, 55 mg. per 100 cc.; blood sugar (fasting), 83 mg. per 100 cc. Urine examination revealed a specific gravity of 1.020, a faint trace of albumin and no sugar. The sediment contained an occasional red and white cell, but no casts. Roentgenograms of the chest and abdomen revealed no abnormalities. The basal metabolic rate was normal.

The patient was maintained on supplementary sodium chloride medication and daily injections of desoxycorticosterone acetate in oil. He showed remarkable improvement; the blood pressure increased to 100/70 mm. Hg, and he gained 2.5 kg. (5.5 lb.) in 12 days. After 12 days of desoxycorticosterone acetate therapy, the following blood determinations were recorded: packed red blood cells (hematocrit), 25.3 per cent; plasma sodium, 136.9 m.eq.; chloride, 105.6 m.eq.; and potassium, 6.2 m.eq. per liter; blood nonprotein nitrogen, 31 mg. per 100 cc. The fasting blood sugar at this time was 80 mg. per 100 cc. After the requirement for desoxycorticosterone acetate had been determined, crystalline pellets of the substance were implanted subcutaneously.

During the following 3 years the progress of the patient was followed carefully; he returned to the Peter Bent Hopkins Hospital regularly for check-up and re-implantation of pellets. Between 1938 and the end of 1942 18 fasting blood-sugar determinations were recorded; all were within normal limits. In addition, two intravenous glucose tolerance tests were performed. During this 3-year period the patient was able to become rather negativistic and at times almost catatonic following moderately prolonged fasting; administration of carbohydrate improved his condition within a period of a few minutes. As a consequence of this, the patient was encouraged to take frequent feedings; by choice he ate an unusually high portion of carbohydrate. Aside from occasional minor intercurrent respiratory infections, the patient was maintained in relatively good health until the end of 1942. In the spring of 1942 the requirement of desoxycorticosterone acetate was estimated as being about 3 mg. daily.

In September, 1942, following a mild upper respiratory infection, the patient failed to eat regularly. He

lost weight and strength rapidly and developed increasing anorexia, lassitude and loss of ambition. The systolic blood pressure fell to 70 mm. Hg from a level of 135-145 mm. Hg. Following administration of adrenal cortex extract, desoxycorticosterone acetate in oil and saline solution parenterally by his local physician, the patient was sent to the Peter Bent Hopkins Hospital on October 4, 1942. Physical examination at this time differed from the original examination 4 years earlier in the following particulars: the pigmentation, while still generalized, was considerably lighter in shade. Blood pressure on admission was 98/74 mm. Hg. Generalized lymphadenopathy was present, with many discrete, shotty 'raisin-sized' nodes palpable in cervical regions, axillae and groin. Laboratory data on this admission disclosed the following: Hb., 93 per cent; red blood cells, 4.4 millions; white blood cells, 5300 with a normal differential. Urinalysis on admission (obtained following intravenous glucose and saline) showed a 3+ sugar. No further urinalyses were performed. Blood chemical findings were as follows: sugar, 212 mg. per 100 cc.; serum chloride, 100 m.eq.; carbon dioxide combining power, 27 m.mol. per liter; and blood urea nitrogen, 11 mg. per 100 cc. Standard metabolic rate was -17 per cent. While in the hospital, the patient's hormone requirement was reassessed, and on Oct. 7, 1942, 5 pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously. The patient's blood pressure gradually rose to 120/84 mm. Hg and the weight to 62.4 kg. (137.3 lb.). The blood sugar of 212 mg. per 100 cc., noted following admission, was assumed to be a laboratory error since on all examinations during the preceding 4 years the fasting blood sugar values had been normal. A second blood glucose determination made in an effort to correct the previous 'error,' was reported as being 309 mg. per 100 cc.!

Following discharge from the hospital, the patient was able to resume his normal activities. One week later, however, he developed a sore throat. Because of this, he was referred to a local hospital where he was given sulfadiazine and supplementary adrenal cortex and desoxycorticosterone acetate in oil. The patient was noted to have glycosuria and ketonuria. The acute infection subsided in 24 hours, but because of the persistent glycosuria and ketonuria he was re-admitted to the Peter Bent Hopkins Hospital for diabetic study.

Physical examination at this time was essentially unchanged from that of the previous admission, except that the pharynx disclosed slight granular injection and the previously noted cervical lymphadenopathy was more marked. Blood pressure at this time was 130/70 mm. Hg. Laboratory data on admission disclosed the following: urinalysis, 4+ sugar, no acetone; Hb., 83 per cent; red blood cells, 4.2 millions; white blood cells, 4500 with a differential of 33 per cent neutrophils, 4 per cent eosinophils, 51 per cent lymphocytes, 6 per cent monocytes and 6 per cent atypical monocyte cells with toxic granules in cytoplasm. Heterophile antibody reaction was negative in all dilutions. The blood chemical findings at the time of admission

TABLE 3. DEVELOPMENT OF DIABETES MELLITUS IN A PATIENT WITH ADDISON'S DISEASE (PATIENT J.H.H.)

	1942				1943					
	Jan.	July	Oct. 4	Oct. 13	Nov. 2	Nov. 15	Dec. 2	Jan. 8	Feb. 4	Ma
Body weight (kg.)	72.0	71.0	61.4	60.4	61.0	60.2	62.2	64.6	68.0	69
(lb.)	158.4	156.2	135.0	132.9	134.2	132.4	136.8	142.1	149.6	151
Blood pressure (mm. Hg)	134/70	125/65	110/70	106/62	110/60	110/76	124/80	110/60	124/80	128
Desoxycorticosterone acetate requirement (mg. per day)	2.5	2.5	2.5	7.5	7.5	6.5	5.5	4.5	4.0	3
Supplementary sodium chloride (gm. per day)	0	2	3	6	0	0	0	0	0	0
Insulin dosage (units per day)					10	20	25	18	18	18
					Diagnosis of diabetes mellitus treatment institute					

were: sugar, 338 mg. per 100 cc.; nonprotein nitrogen, 23 mg. per 100 cc.; total protein, 5.4 mg. per 100 cc., (albumin, 2.3 gm.; globulin, 3.1 gm.); cholesterol, 195 mg. per 100 cc.; chloride, 99 m.eq., and carbon dioxide combining power 21 m.mol. per liter. Twenty-four-hour ketosteroid excretion was 2.6 mg.

#### METHODS

During this study, the patient was fed a diet of standard composition (protein 83 gm., fat 112 gm., carbohydrate 220 gm. The caloric content of this diet was 2220). The standard diet was given for at least 2 days prior to each test period. On the day preceding glucose tolerance tests or studies of respiratory metabolism, the patient was given a relatively small dose (8 units) of regular insulin with his morning meal; no further insulin was administered until the following day, after completion of the test.

For a period of several weeks prior to these studies the patient was trained for respiratory metabolic studies. On each test day, following a 13-hour fast, expired air was collected for a 10-minute period in a Collins chain-compensated gasometer. Air samples were analyzed in duplicate for carbon dioxide and oxygen content on a Haldane-Henderson gas analyser. Standard metabolism was calculated; urinary

nitrogen excretion was determined; and differential derivation of calories was carried out with the aid of Lusk's table (20). A standard intravenous glucose tolerance test (21) was made before and after the administration of 100 mg. of 11-dehydro-17-hydroxycorticosterone. During the test periods the daily urinary excretion of glucose, acetone, nitrogen (Kjeldahl), phosphorus (22), potassium (23), sodium (24) and chloride (25) were determined. Blood sugar determinations were made according to the method of Folin-Malmros (26).

#### OBSERVATIONS

The onset of diabetes mellitus in this patient with Addison's disease previously well controlled with synthetic desoxycorticosterone acetate therapy, was characterized by progressive and unexplained anorexia, weakness, weight loss, fall in blood pressure and increased hormone requirement (table 3). A review of laboratory data collected during the 4 years preceding the onset of diabetes revealed no significant increase in fasting blood-sugar values during this period (table 4). The period of 1938-1942 was characterized by frequent bouts of spontaneous hypoglycemia which occurred particularly during the course of intercurrent infections, following prolonged fasting or following strenuous exercise. This patient, however, did not have a hypoglycemic episode precipitated by the administration of intravenous glucose as so frequently occurs in patients with Addison's disease (21). It is noteworthy that the glucose curve in 1939 and 1940 (fig. 1) returned to normal somewhat more slowly than is usually the case in normal subjects and in patients with Addison's disease. A progressive decrease in glucose tolerance was

TABLE 4. FASTING BLOOD-SUGAR VALUES, MAY, 1938, TO FEBRUARY, 1942, PATIENT J. H. H.

	1938	1939	1940	1941	February 1942
Blood sugar, mg. per 100 cc. (average and range)	90 78-102	87 80-100	95 93-98	89 81-100	88 82-93
Number of determinations	9	8	5	4	2

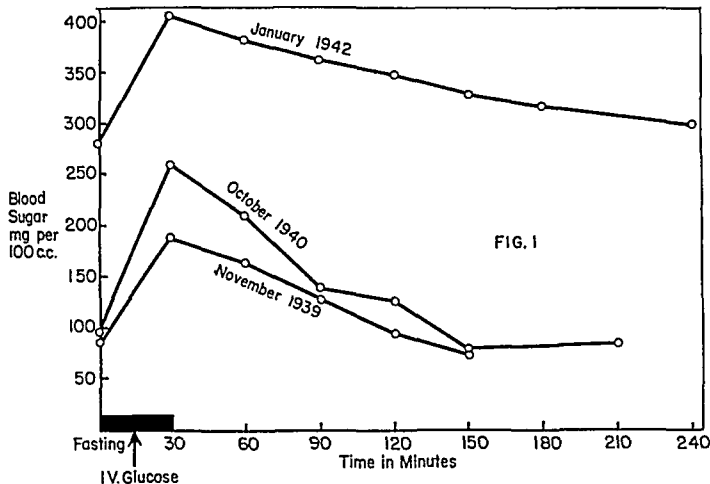


FIG. 1. Intravenous glucose tolerance tests in Addison's disease (patient J. H. H.). 0.5 gm. of glucose per kg. of body weight.

observed between 1939 and 1940 (fig. 1). The onset of diabetes mellitus was associated with a further decrease in glucose tolerance (1943). During the years 1938 to 1942, this patient subsisted on a diet which was almost exclusively carbohydrate, although not exceptionally high in calories.

On admission to the Peter Bent Brigham Hospital, Oct. 4, 1942, the patient was found to be dehydrated and to have a moderate decrease in blood pressure (table 3), although the size and number of pellets of synthetic hormone implanted subcutaneously appeared to be adequate. During the initial period of dehydration prior to admission to the hospital ketonuria had been observed. With supplementary injections of desoxycorticosterone acetate in oil<sup>3</sup> rehydration occurred and a rise in blood pressure followed. At this time spontaneous ketonuria was minimal or absent despite the continued excretion of rather large quantities of glucose (50-100 gm. daily). It appeared that ketone production exceeded ketone utilization in this patient with Addison's disease and diabetes mellitus only during periods of severe dehydration or during the course of intercurrent infections.

The striking effect of insulin treatment of blood-sugar levels and renal excretion of glu-

cose, nitrogen, phosphate and potassium is demonstrated in figure 2. Insulin withdrawal was accompanied by an increase in glucose excretion and presumably an increase in glucose formation from endogenous protein sources as evidenced by the increased excretion of nitrogen, phosphorus and potassium. Ketonuria did not occur. Blood-ketone determinations were not made.

Insulin sensitivity was especially noteworthy in this patient as illustrated by the following episode. After determining that the fasting blood-sugar level was 350 mg. per 100 cc., 10 units of insulin was administered, following which a breakfast containing carbohydrate 88 gm., protein 23 gm. and fat 44 gm. was given. At noon 5 units of insulin was given prior to a lunch which contained carbohydrate 52 gm., protein 25 gm. and fat 31 gm. At 3:00 p.m. the patient was found to be in a stupor from which he could not be roused. Intravenous glucose administration resulted in prompt recovery. Thus despite a fasting blood-sugar level of 350 mg. and the administration of a total of 140 gm. of carbohydrate at breakfast and lunch, this patient developed hypogly-

<sup>3</sup> Desoxycorticosterone acetate in oil (Percorten) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

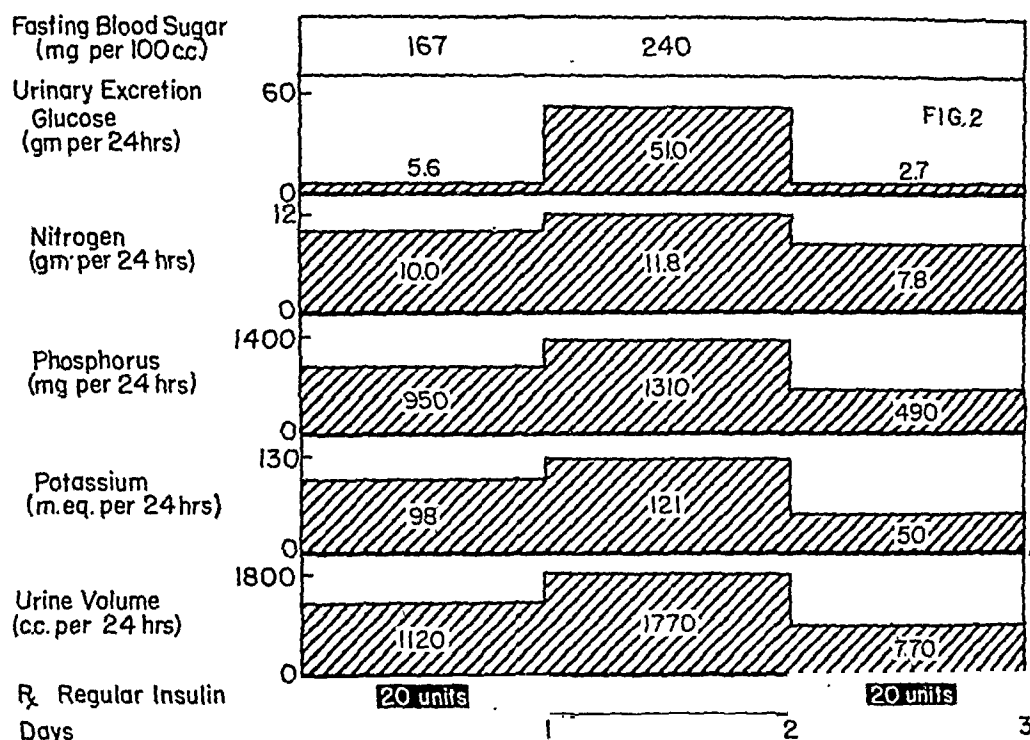


FIG. 2. Effect of insulin withdrawal on renal excretion of glucose, nitrogen, phosphorus and potassium (patient J. H. H.). Diet, gm.: carbohydrate, 220; protein, 83; fat, 117.

cemia following the administration of 15 units of regular insulin (10 units prior to breakfast and 5 units prior to lunch).

An interesting and unusual reaction occurred in this patient during the initial period of insulin administration and following large supplementary injections of desoxycorticosterone acetate and supplementary sodium chloride medication. This was characterized by a rapidly developing paralysis of the muscles of both lower legs and feet. There was no pain and no evidence of disturbance in sensation or reflexes. A provisional diagnosis of 'low-potassium paralysis' was entertained, and appeared to be confirmed by the low level of serum potassium which was observed at that time (3.46 m.eq. per liter) and by the striking improvement which followed administration of potassium citrate. Paralysis of this nature has been observed in a patient with Addison's disease who was treated with excessive doses of desoxycorticosterone acetate and supplementary sodium chloride following nephrectomy (27) and in normal dogs receiving large doses of desoxycorticosterone acetate (28). It is possible that in this patient the shift of potassium from the serum following insulin administration in the presence of a high blood-sugar level (29, 30)

may have augmented the effect of excessive desoxycorticosterone acetate and sodium chloride therapy.

A marked improvement in appetite followed the institution of insulin therapy. Prior to the development of diabetes this patient's appetite had been poor and finical. He had consumed, by choice, a diet composed almost entirely of carbohydrate; the maintenance of an adequate protein intake had been a major problem. Following the onset of diabetes, however, the appetite increased and he displayed a fondness for fatty foods. His weight increased approximately 10 kg. (22 lb.) in 5 months.

The development of diabetes mellitus in this patient was accompanied by a dramatic alteration in personality and outlook on life. During the 4 years prior to the onset of this complication, he had been noted to be a taciturn, shy, introverted individual who intentionally limited his contacts with strangers and new situations to the barest possible minimum. His withdrawal had been noted to be most marked following prolonged fasting, at which times he became definitely negativistic and almost catatonic in attitude. Since the onset of diabetes mellitus, however, he has overcome to a considerable extent his avoidance of challeng-

ing situations. Whereas in the past it had been difficult to arouse or hold his interest in any activities not directly relating to himself, he now displays a moderate degree of spontaneous enthusiasm.

Despite the continued high levels of blood sugar, this patient's abnormal electro-encephalographic pattern (31) has not revealed significant improvement. It is possible that in this patient the maintenance of a high blood-sugar level without normal capacity to utilize glucose may be a factor in perpetuating the abnormalities previously observed. It is also possible of course that the changes previously reported may be permanent in nature. It is of interest to note that the improvement in the patient has not been reflected in a measurable alteration in electro-encephalographic pattern. During the course of the illness, slight changes in the configuration of the electrocardiogram of this patient have been noted. These have been interpreted as of no clinical significance, however, and have shown no relation to the onset of diabetes mellitus. Heart size, as measured by the teleroentgenogram, has varied with the patient's clinical state and hormone level, but has shown no significant alteration since the onset of diabetes.

### *Changes Accompanying the Administration of 11-Dehydro-17-Hydroxycorticosterone (Compound E, Kendall)*

The administration of a single dose of 33 mg. of 11-dehydro-17-hydroxycorticosterone<sup>4</sup> (compound E, Kendall) in oil was followed by a striking decrease in glucose tolerance as measured by the intravenous glucose tolerance test (fig. 3). A balance study made during the period of compound E administration revealed a marked increase in glucose, nitrogen and phosphorus excretion (fig. 4). It is also of interest to note that there was an increase in sodium and chloride excretion with compound E treatment (32). No increase in potassium excretion was observed (fig. 4), whereas a striking increase in potassium excretion accompanied insulin withdrawal (fig. 2). A decrease in respiratory quotient and a striking change in basal caloric distribution was induced by the administration of compound E (fig. 5). These changes have been compared (fig. 5) with those observed in a patient with uncomplicated Addison's disease and a normal human subject treated with the same quantity of compound E (33 mg.). In all 3 individuals there was a rise

<sup>4</sup> Kindly supplied by Dr. E. C. Kendall of the Mayo Clinic, Rochester, Minnesota.

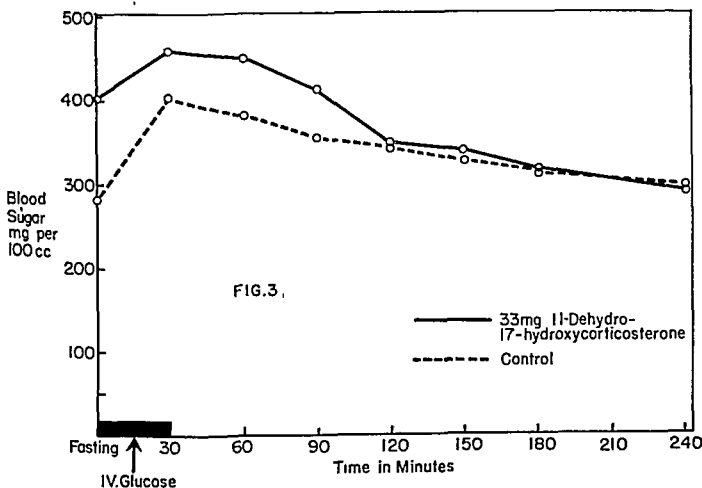


FIG. 3. Effect of 11-dehydro-17-hydroxycorticosterone on intravenous glucose tolerance (patient J. H. H.). 0.5 gm. of glucose per kg. of body weight.

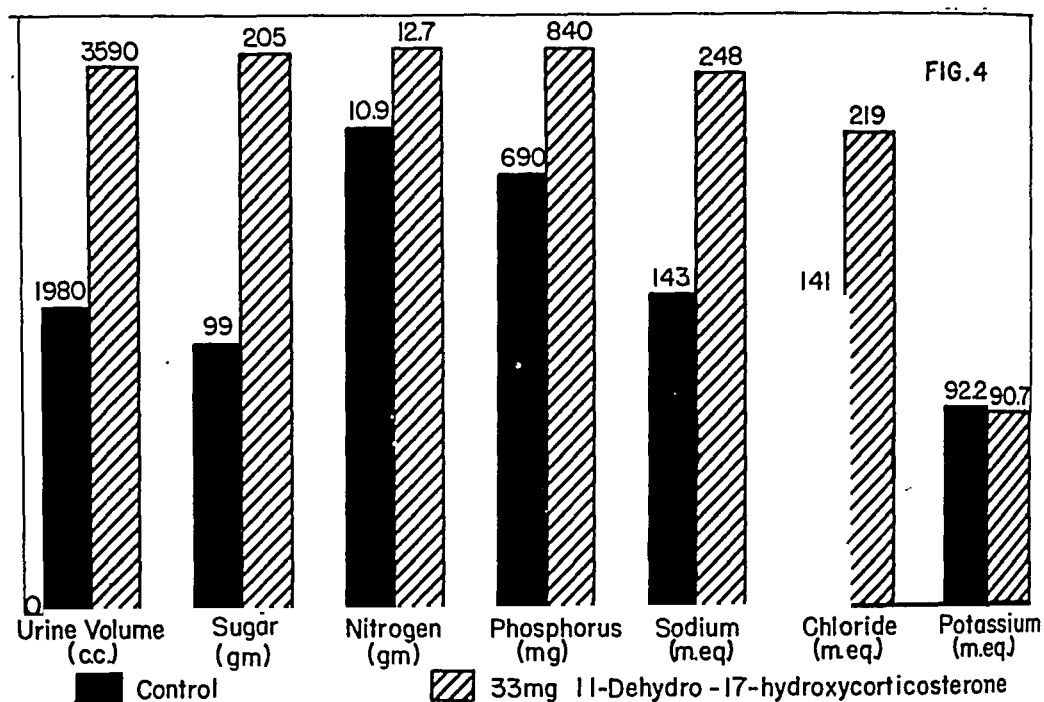


FIG. 4. Effect of 11-dehydro-17-hydroxycorticosterone on 24-hour renal excretion (patient J. H. H.). Diet, gm.: carbohydrate, 220; protein, 83; fat, 117. Regular insulin, 8 units daily.

in fasting blood-sugar level and a striking decrease in fasting nonprotein respiratory quotient. In both patients with Addison's disease there was a definite increase, following the administration of compound E, in basal oxygen consumption. This change did not occur in the normal subject (fig. 5).

#### DISCUSSION

A unique opportunity to study the mechanism of the alterations of carbohydrate metabolism in Addison's disease and diabetes mellitus was presented by the development of the latter disease in a patient with Addison's disease who had been under careful observation for a period of 4 years. The earliest evidences of a diabetic trend in this patient were *a*) maintenance of normal fasting blood-sugar values, and *b*) failure to develop hypoglycemia following intravenous administration of glucose (21). Later there was definite evidence of decreased glucose tolerance as indicated by the blood-sugar curve following glucose administration (fig. 1, year 1940).

It has been suggested (17, 18) that the development of spontaneous hypoglycemia in the absence of adrenal cortical hormone results from an impairment of gluconeogenesis. Furthermore, the relatively high nonprotein respiratory quotient in patients with Addison's dis-

ease suggests an impaired ability to utilize (21). In the presence of combined diabetes mellitus and Addison's disease, however, it appears that utilization of fat is not impaired as at least 60 per cent of basal calories were derived from fat in this patient on several occasions. Despite the relative severity of diabetes, ketonuria in this patient was minimal at all times as long as hydration was maintained with adequate desoxycorticosterone therapy. It cannot be stated whether absence of ketonuria reflected decreased ketone formation from fat and protein or increased ketone utilization with or without an increased renal threshold for ketone bodies. Rather severe ketosis has been reported in several cases of concurrent diabetes mellitus and Addison's disease (1, 2, 3). A review of the data presented, however, revealed that ketonuria was observed only in the presence of dehydration or intercurrent infection.

The development of diabetes mellitus in this patient enabled him to maintain high blood-sugar levels during prolonged fast; therefore it would appear that the inability of patients with uncomplicated Addison's disease to maintain an adequate blood-sugar level cannot be explained entirely on the absence of adrenal cortical hormone, since increased gluconeogenesis was observed without any increase

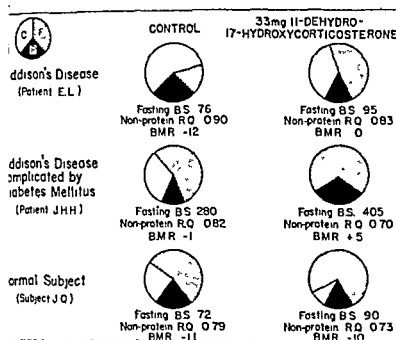


FIG. 5. Effect of 11-dehydro-17-hydroxycorticosterone on fasting blood-sugar level and caloric distribution.

renal cortical hormone when diabetes super-  
vened.

The alterations in metabolism observed in this patient following the administration of 33 g. of compound E confirm the observations of Ingle and Thorn (33) on the action of adrenal cortex preparations containing an oxygen atom at C. 11. The marked increase in fasting blood-sugar levels and increased renal excretion of nitrogen and phosphorus observed following administration of this substance (fig. 4) suggests that it initiates increased gluconeogenesis. The alteration in the glucose tolerance curve following compound E administration suggests that this compound also inhibits glucose utilization or storage. A marked increase in the 24-hour renal excretion of sodium and chloride occurred. Potassium excretion, on the other hand, was not altered. It is possible that the unchanged renal excretion of potassium following compound E therapy reflected the neutralizing effect of two antagonistic actions of this hormone, a) the increased rate of potassium liberation from protein break-down, as evidenced by increased excretion of nitrogen and phosphorus, and b) the possible action of the hormone in increasing the renal tubular re-absorption of potassium. In addition to promoting increased gluconeogenesis, compound E treatment appeared to alter fat metabolism in this patient. Fasting respiratory metabolism studies indicated that a marked lowering of nonprotein respiratory quotient occurred, and that the percentage of calories derived from fat increased significantly (fig. 5). A considerable

degree of ketonuria was present following compound E therapy, whereas otherwise it was minimal or absent.

Because of the high degree of insulin sensitivity which this patient presented it was felt that the administration of protamine zinc insulin might be unwise. With the use of regular insulin, it was possible to delay insulin administration until immediately prior to beginning a meal. Another mechanism which protected this patient against excessive administration of insulin was the return of his negativistic attitude when the blood-sugar level was low. As a consequence of this, he refused to take or to be given any medication (including insulin) at this time, whereas he was perfectly willing to do so when the blood sugar was higher and his disposition consequently more amiable.

#### SUMMARY

A second case of diabetes mellitus developing in a patient with well-established Addison's disease has been described. The onset of diabetes mellitus in this patient with previously well-controlled Addison's disease was characterized by anorexia, loss of weight, lassitude, fall in blood pressure and increased requirement of desoxycorticosterone acetate. Institution of insulin therapy at a time when large doses of desoxycorticosterone acetate and sodium chloride were being administered precipitated the development of 'low potassium' muscular weakness. Regulation of diabetes with small doses of insulin was followed by striking improvement in appetite, desire for fatty foods, increased weight, restoration of blood pressure and general sense of well-being. Marked improvement in personality was observed in conjunction with the persistent hyperglycemia. No change in the abnormal electro-encephalogram was noted. Withdrawal of insulin was followed by an increased blood-sugar level, and an increased excretion of nitrogen, phosphorus and potassium. With adequate desoxycorticosterone acetate, which prevented excessive dehydration, no return of ketonuria was observed during the aggravation of diabetes induced by insulin withdrawal. The marked insulin sensitivity of this patient suggests that protamine zinc insulin administration might prove to be extremely hazardous. The administration of a single dose of 33 mg.



of 11-dehydro-17-hydroxycorticosterone was followed by an elevation in blood-sugar level, a lowering of nonprotein respiratory quotient, increased excretion of glucose, nitrogen and phosphorus accompanied by the presence of ketonuria and increased excretion of sodium and chloride. It appears from studies on this patient that the inability of patients with uncomplicated Addison's disease to maintain an adequate fasting blood-sugar level is not dependent solely upon deficiency of the adrenal cortical hormone.

The authors express their appreciation to Dr. John T. Quinby, Miss Marion J. Brian, dietician, and Mrs. Grete Heinemann, technician, for their assistance, and to patient J. H. H. for his continued co-operation throughout this study.

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# Diabetes Mellitus Associated with Hirsutism and Unusual Insulin Resistance

## CASE REPORT

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THE ASSOCIATION in women of diabetes mellitus and beards was first described by Achard and Thiers (1) in 1921. Since that time much interest has developed in clinical pictures displaying these among other symptoms, and considerable controversy has arisen concerning the etiologic factors underlying these findings. The following case report not only demonstrates the problems in diagnosis of unusual features in carbohydrate tolerance well.

### CASE REPORT

Mrs. J. L. E., a 58-year-old Jewish widow, para 0-0, was first seen in the Metabolic Clinic of Charity Hospital on Sept. 17, 1937. The presence of glycosuria and a blood sugar of 275 mg. per cent led to a diagnosis of diabetes mellitus. The patient was regulated on 20 units of regular insulin once daily, but the insulin requirements as denoted by glycosuria and hyperglycemia, gradually rose until, in 1940, the patient was taking a total dosage daily of 260 units of crystalline insulin. She was then changed to a combination of protamine and crystalline insulin totalling 190 units daily. Later she was maintained on the unusually high dosage of 195 units of protamine insulin daily, which as continued until she was admitted to the hospital on March 16, 1942, for re-evaluation of the virilizing syndrome and of the diabetes mellitus. Throughout this period in the clinic she was maintained on a diet of 1330 calories with 150 gm. of available glucose. Persistent glycosuria and frequent mild acetoneuria were noted, but no symptoms of diabetic acidosis ever developed. The decreasing carbohydrate tolerance, as determined by standard glucose tolerance tests, is graphically shown in figure 1, which reveals the progress of the diabetes mellitus in the period from 1940 to 1942.

At the time of admission to the hospital on March 16, 1942, the patient (fig. 2-4) manifested virilism, hypertension, plethoric facies, obesity confined chiefly to the torso, amenorrhea, genital regression—all of several years' duration—and diabetes mellitus which, as noted above, had been observed for 5 years. Family history, developmental history and past history were non-contributory. Menarche occurred at 18 years, periods were regular every 28 days, with 3 days of scant flow. Dysmenorrhea had occurred occasionally on the day preceding onset of menstrual flow. Menopause occurred at the age of 35, presumably of physiologic origin. The patient was married at the age of 32. Libido and sexual compatibility were apparently present. No pregnancies resulted. Her husband was killed when the patient was 44 years old. The patient stated that she had always been chubby and short and that some hirsutism dated since early childhood. She shaved her face two or three times weekly and, in her opinion, the degree of hirsutism had not deepened recently. Patient did not tire easily, perspired freely and had oily hair. She had never taken any endocrine preparations other than insulin.

A general endocrine survey was made. The patient was a short, obese, white female of age 58. A blood pressure of 140/80 mm. Hg was recorded. At times it reached 190/100. The obesity was symmetrically distributed with a tendency to greater distribution on the trunk than on the extremities. Skin was moderately oily and of a reddish hue, but was judged to be of normal texture and consistency. The thyroid gland was slightly palpable. Considerable hirsutism was present on lips, face, trunk, back, sacral area and extremities. A definite pubic escutcheon of the masculine type was noted with a ridge of coarse black hair extending to the umbilicus. The hair in general was wiry, dark and luxuriant in growth. No striae were noted. Breasts were poorly developed with considerable fatty tissue and scant glandular tissue. The vaginal and rectal examinations revealed the pubic hair as described above, very small labia minora, dry, non-succulent vaginal mucosa, partially atrophic vaginal canal and

mitting one finger with ease, small, freely movable cervix and uterine body, and normal adnexa. The clitoris was not hypertrophied.

In an effort to demonstrate an etiologic basis for the above manifestations, the following studies were instituted: lateral view of the sella turcica, visual fields and eye grounds, roentgen views of skull and vertebrae for evidences of osteoporosis, chest film, basal metabolic determinations, excretory urography, peri-renal insufflation. No abnormalities were revealed. Basal metabolic determinations varied from +10 to +14. Blood cholesterol was 232 mg., urea 15.7 mg.; CO<sub>2</sub> combining power of the blood ranged from 42 to 56 vol. per cent on 11 consecutive determinations. Urinal-

cially before the noon meal. The early morning specimens of urine usually manifested a 1+ reaction for glucose.

In view of the presence of disturbed carbohydrate metabolism and the lack of a definite etiologic basis for the clinical picture, roentgenologic therapy to pituitary gland was considered. Throughout the period from April 6 to April 27, 1942, the patient received total of 2400 r. applied through two lateral portals: glucose tolerance curve was established prior to irradiation and repeated at the conclusion of therapy (fig. 1). At the conclusion of the roentgenologic treatment, no change was noted in the daily glycosuria; acetonuria had been definitely reduced to an oc-

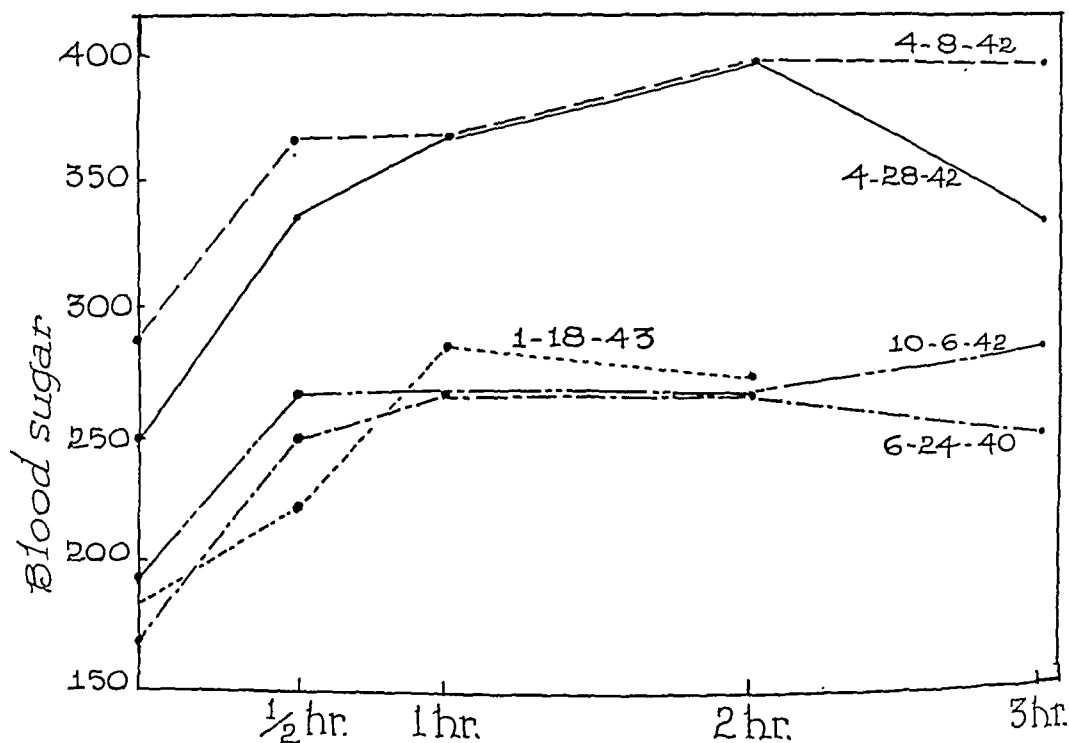


FIG. 1. Standard glucose tolerance tests in 58-year-old woman with diabetes mellitus, virilism and resistance to insulin.

ysis showed glycosuria and occasional mild acetonuria, but revealed no evidences of kidney impairment. Hematologic studies were within normal limits. No hormonal titrations were made.

A series of metabolic observations concerning the diabetes mellitus were recorded and all insulin was discontinued. At that time the patient was taking 195 units of protamine zinc insulin daily. The diet of 1330 calories was continued. There was very little effect from the discontinuation of the insulin. During the following 12 days, the patient spilled 1+ and 2+ sugar qualitatively. On March 28, 1942, the diet was increased to 174 gm. of available glucose with 1610 calories and maintained at that level for the remainder of her stay in the hospital. Whereas traces of acetone had been noted three times during the preceding 12 days, the increase in diet resulted in a more frequent positive reaction for acetone without clinical acidosis, accompanied by a 3+ and 4+ reaction for glucose, espe-

sionally before the noon meal. The early morning specimens of urine usually manifested a 1+ reaction for glucose.

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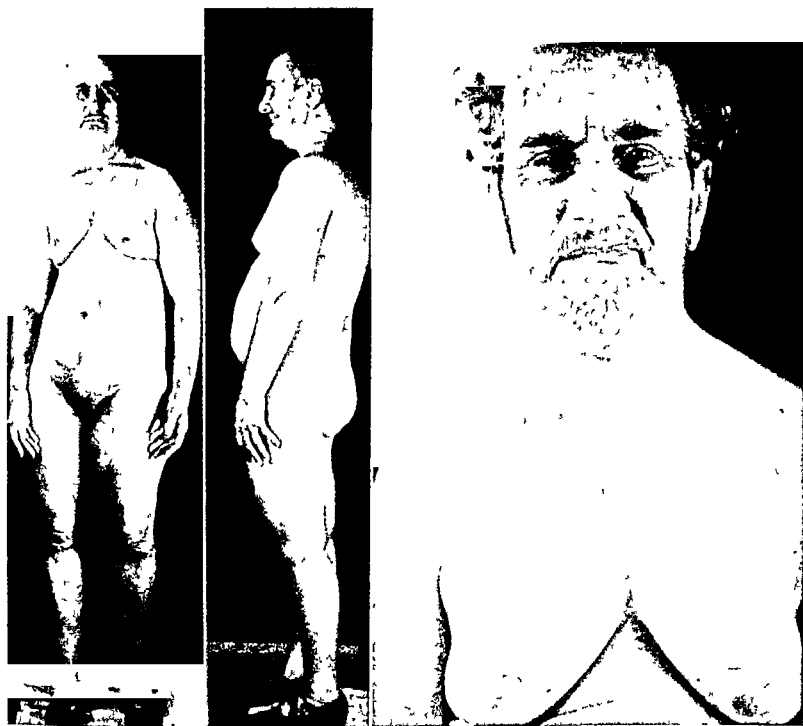
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#### DISCUSSION

The data derived from this patient fulfill present-day criteria for the diagnosis of func-



FIGS. 2, 3, 4 Appearance of 58-year-old woman with diabetes mellitus, virilism, plethoric facies and obesity confined chiefly to the trunk

betes mellitus. However, the rôle of malfunction of many organs, especially the hypophysis, thyroid, liver, and adrenals as well as the adrenals, in the disturbance of carbohydrate metabolism which is interpreted as diabetes mellitus, demands an evaluation of the diabetic patient from the standpoint of evidence of disease in these organs.

In 1932 Cushing (2) described the syndrome commonly called pituitary basophilism. The clinical characteristics of this syndrome, as described by Cushing, are as follows: a rapidly acquired and often painful obesity limited chiefly to the face, neck and trunk, but usually sparing the extremities, producing the so-called 'buffalo type' of obesity, cervico dorsal kyphosis, occasionally with a decrease in stature, regression of the sexual organs in women with associated amenorrhea, sterility and loss of libido; hirsutism, in particular on the face and

trunk, resembling somewhat a masculine distribution of hair; a dusky, plethoric appearance of the skin, often with purplish striae on the lower part of the abdomen and medial aspects of the thighs, and occasionally accompanied by acrocyanosis and ecchymosis of the extremities; facial changes which make the eyes appear small and slit-like, producing the so-called 'pig eyes', hypertension, polycythemia; glycosuria; osteoporosis, particularly of the vertebrae, resulting in vague lumbosacral pains, and, if the carbohydrate tolerance is sufficiently disturbed, the clinical features of diabetes mellitus, such as fatigability and muscular weakness, polyphagia, polyuria, polydipsia, hypercholesterolemia, dryness of skin, and visual disturbances resulting from alterations in water balance. Two of the 14 verified cases reported by Cushing (3) occurred in men.

Although this syndrome has been widely rec-

ognized, its cause is determined with difficulty and, in individual cases, it is frequently impossible to establish the etiologic factor. Cushing (2) believed that this typical syndrome was associated with basophilic adenomata of the pituitary gland. Pardee (4) noted hyperplasia instead of adenomata, and Fuller (5) observed the association of the syndrome with a chromophobic adenoma of the pituitary. Susman (6) discovered non-clinical basophilic adenomata of the pituitary in 3 per cent of routine autopsies.

Moehlig and Bates (7) advanced the theory that the primary pathologic disturbance existed in the adrenal cortex and that basophilic infiltration in the pituitary gland was secondary. Indeed the clinical features of the syndrome have been related to adenomata, carcinomata and hyperplasia of the adrenal cortex by Turney (8), by Kepler and group (9), by Hare and associates (10), by Calder and Porro (11), by Oppenheimer and co-workers (12) and others. The studies of Long (13) and others have shown that the adrenal cortical hormone promotes gluconeogenesis and the conversion of proteins into sugar. From these observations, Albright and co-workers (14) suggest that the diabetes mellitus of Cushing's syndrome may be ascribed to hypergluconeogenesis.

Although Calder and Porro (11) attached significance to hypertrophy of the clitoris as being suggestive of the adrenal form, Oppenheimer and Silver (15) concluded that there were no clinical findings by which patients with Cushing's syndrome due to pituitary basophilism could be distinguished from those in whom the syndrome was due to adrenal cortical involvement. Metabolic studies have yielded few significant data. Hormonal titrations of blood and urine have been investigated extensively, but, by themselves, do not permit accurate differentiation. In general, increased androgenic values (17-ketosteroids) of the urine accompany the syndrome (14, 16, 17, 18, 19, 20), the chief androgen excreted appearing to be dehydroisoandrosterone derived presumably from the adrenal cortex (20). The differential diagnosis of Cushing's syndrome has been reviewed in detail in a recent article by Dorfman, Wilson and Peters (16).

The present patient showed many of the findings characteristic of Cushing's syndrome—

obesity, changes in the sex organs, hirsutism, plethoric appearance of the skin, hypertension and a disturbed carbohydrate metabolism. D calcification of bones, polycythemia, striae or severe hypertension are lacking. Although the absence of the latter findings does not exclude the diagnosis of Cushing's syndrome, the incompleteness of the picture, together with the absence of evidence of enlargement of the pituitary or adrenal glands, makes the diagnosis a doubtful one. It is possible that in the future the patient may develop added findings which will make the diagnosis of Cushing's syndrome conclusive. Such evidence, or histologic study of the gland, would be necessary for final decision.

Virilizing phenomena may be related to other disturbances. Leyton, Turnbull and Bratto (21) observed such findings in a patient with carcinoma of the thymus. Silver (22) added pineal tumors. R. Meyer and others have emphasized the association of virilizing phenomena, without hypertension and metabolic disturbances, with arrhenoblastoma of the ovary. The present case does not seem to fit into any of these categories.

Hirsutism with or without obesity occurs in a considerable number of patients on the basis of hereditary or unknown causes. No hereditary factors were found in the case of our patient. Unknown causes undoubtedly include both adrenal and pituitary disturbances in which criteria for diagnosis are inadequate. The faulty carbohydrate tolerance favors such a possibility. Through the work of Houssay it is well known that the anterior pituitary gland may exert a marked influence on carbohydrate metabolism. Extracts of the anterior pituitary gland have produced diabetic states in normal experimental animals and anti-insulin activity has been found in the urine of patients with Cushing's syndrome with diabetes (23). Eosinophilic adenomata of the anterior pituitary are sometimes associated with diabetes mellitus.

A most interesting and striking finding in our patient is the effect of insulin on the disturbance in carbohydrate metabolism. The ability of this patient to receive 260 units of crystalline insulin daily without any particularly pronounced effect upon the carbohydrate metabolism and without the development of insulin reactions has been interpreted as a state of insulin re-

sistance. Just as striking was the lack of change in carbohydrate metabolism with discontinuation of the insulin. Unfortunately no insulin sensitivity test, such as described by Himsworth and Kerr (24), was made. These workers also found insulin insensitive types of diabetes in two patients with Cushing's syndrome. In one, roentgen irradiation of the pituitary region was followed by clinical improvement as well as improvement in the patient's sensitivity to insulin. Fraser, Albright and Smith (25) also found the hyperglycemia of Cushing's syndrome resistant to insulin therapy. Himsworth and Kerr noted further that insulin-insensitive patients fall, in general, into a clinical group different from that of the insulin-sensitive cases. Insulin-sensitive diabetic patients tended to be relatively young, thin, with normal blood pressure and arteries, easily developing ketosis and marked reactions to insulin. The insulin-insensitive group was older, obese, hypertensive and arteriosclerotic. They tolerated over-dosage of insulin well without hypoglycemic symptoms and rarely developed ketosis. Certainly our patient had these latter characteristics. Himsworth and Kerr interpreted their data on the glucose tolerance and the insulin glucose tests to indicate that insulin-sensitive diabetes resulted from lack of insulin while insulin-insensitive diabetes resulted, not from lack of insulin, but from impaired action of insulin. These patients have a number of characteristics in common with the obese 'diabetics' described by Newburgh (26).

The mechanism of insulin insensitivity is not understood. The possible rôle of the anterior pituitary gland has already been mentioned. The frequent development of insulin resistance with infection and other conditions (24) has led to the idea that endogenous insulin production by the pancreas is diminished. Greene, David and Johnston (27) have shown that this concept is not necessary for the explanation. They depancreatized dogs and stabilized them on diets and insulin. Varying degrees of insulin resistance developed from injections of bacteria, irritating substances, and, in one instance, spontaneously. Since no endogenous insulin was produced in these animals, endogenous insulin could not enter into the explanation of insulin resistance. A reduced effectiveness of insulin, mechanism not yet determined, obviously was

the cause.

In instances in which the causative lesion cannot be definitely demonstrated for Cushing's syndrome, Freyberg, Barker, Newburgh and Collier (28) recommend irradiation of the pituitary gland, a view shared by Bromley (29) and others. As a result of our failure to demonstrate a definite etiologic basis for the syndrome in this patient and because of the possibility that pituitary disease might play a part in its development, roentgenologic therapy was applied to the pituitary gland. From a study of figure 1, it will be observed that a gradually increased impairment of carbohydrate tolerance existed in this patient throughout the period from 1940 to the time of admission to the hospital in 1942. The clinical demands for increasing dosages of insulin may be used partially to substantiate this view, although the insulin resistance interferes with this interpretation.

Following roentgenologic therapy to the pituitary gland, two observations by standard glucose tolerance tests in the past 10 months have revealed definite improvement in the carbohydrate tolerance. It is to be recalled that no insulin has been given during the past year. Qualitative and quantitative observations of glycosuria and acetonuria over this period of time have supported this assumption. Some of the improvement in the carbohydrate tolerance may have resulted from, or be related to, the fact that the patient experienced a considerable weight loss for 6 months following roentgenologic therapy, in spite of the fact that the diet had been increased gradually to 1940 calories from 1330 calories, which had been maintained throughout the preceding 5 years without effect on weight.

In the past 3 months, the patient's weight has been stabilized. It is not clear whether the weight loss resulted from direct improvement as a result of roentgenologic therapy to the pituitary gland or whether the sudden cessation of insulin may have prompted it. Evidence against the latter view is found in the fact that the carbohydrate tolerance, as measured by the glucose tolerance test, appears to be definitely improved. Additional objections to acceptance of the apparent improvement in the carbohydrate tolerance of this patient as a consequence of roentgenologic therapy of the pituitary gland lie in the facts that no definite diagnosis of pi-

pituitary basophilism can be established and that the diabetes mellitus is not cured, but only improved. Whether the patient would have manifested similar findings without any roentgenologic therapy to the pituitary gland, or whether additional roentgenologic therapy is indicated with the hope of further improving the carbohydrate tolerance, is conjectural. Certainly no other evidences of improvement of the findings other than carbohydrate tolerance and weight loss have been noted.

# SUMMARY

A patient exhibiting hirsutism and disturbed carbohydrate metabolism has been presented with the purpose of emphasizing the protean picture of disease encompassed by these findings, the pluriglandular aspects of diabetes mellitus, a remarkable degree of insulin resistance and 'indifference,' and the apparent improvement in carbohydrate metabolism that may follow irradiation of the pituitary gland in carefully selected cases.

The authors wish to express their appreciation to Dr. Manuel Garcia of the Department of Radiology, Tulane University and Charity Hospital of Louisiana at New Orleans, for his kind cooperation in the roentgenologic therapy of this patient.

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# Serum Phosphatase Activity in Hyperparathyroidism

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INTEREST in the metabolism of phosphorus and particularly the relationship of inorganic phosphate to phosphoric esters has been steadily increasing since Grosser and Fusler (1) discovered that hydrolysis of such esters in the animal organism is governed by an enzymatic system.

Although phosphatase activity is exhibited by a variety of tissues, the greater part of investigative work has been centered on the rôle of phosphatase in the metabolism of bone. It has been determined that the phosphatase involved shows optimum activity at pH 9 to 10.5, and thus might properly be termed alkaline phosphatase.

Quantitative phosphatase studies on tissue may be made by various means such as specific staining technique and tissue extraction. While such procedures permit excellent comparative studies on specific tissue, they are not generally adaptable for clinical laboratory work due to the inaccessibility of most of the tissues involved. However, marked variations in local phosphatase activity are commonly reflected in the phosphatase content of the serum, and its quantitative determination in whatever arbitrary units one may choose may be of considerable significance in the diagnosis of a number of clinical disorders.

It is interesting to speculate on the source of the phosphatase in serum. Bone most likely supplies the major part since an appreciable reduction does not occur after the removal of other organs containing phosphatase. Moreover, Robison (2) has found that phosphatase activity is high in growing bone and cartilage.

Markedly increased osteoblastic activity may reflect itself in correspondingly increased phosphatase levels in the serum. Kay (3) and many other workers have recorded quantitative serum phosphatase determinations in a number of bone diseases, including metastatic carcinoma to bone from various organs.

Davies (4) demonstrated in liver and spleen the presence of a different phosphatase with an optimum pH of approximately 5. This phosphatase has been generally termed 'acid' in contradistinction to the 'alkaline' phosphatase previously observed. Its physiological action has not been definitely determined. Among other organs rich in acid phosphatase the prostate has assumed great importance since the discovery that disseminated carcinoma of this gland is frequently attended by high acid phosphatase levels in the blood. Huggins and Hodges (5) have used phosphatase determinations as a quantitative measure of neoplastic activity of prostatic cancer as affected by sex hormones. At the present time a serum-acid-phosphatase value exceeding 10 King and Armstrong units is usually considered diagnostic of carcinoma of the prostate with skeletal metastasis. It should be emphasized that significant increases in blood phosphatase do not occur while the neoplastic growth is confined within the gland itself.

In view of the high content of acid phosphatase in the normal prostate, it is logical to assume that the source of the increased acid phosphatase in blood in disseminated carcinoma of the prostate is metastatic prostatic tissue. That other sources of acid phosphatase in blood exist



is evident from the fact that it is present normally in small amounts. Gutman and Gutman (6) investigated acid and alkaline phosphatase activity in a number of miscellaneous diseases including many with marked elevation of alkaline phosphatase. In their series of cases only patients with carcinoma of the prostate with bony metastases exhibited high acid phosphatase in the blood.

Within the last year we have had the opportunity to study an 18-year-old girl suffering from hyperparathyroidism due to a solitary adenoma of a parathyroid gland. The diagnosis was confirmed by microscopic examination of the adenoma following its surgical removal. The alkaline phosphatase values in the serum were very high and increases in the acid phosphatase levels of a magnitude hitherto only reported in disseminated prostatic carcinoma were present. To be certain that the increases really represented a 'peak' in the acid range, we determined the phosphatase activity by the King and Armstrong (7) method at pH of 4, 5, 6, and 9.5.

The following values given in King and Armstrong units were found:

TABLE 1. PHOSPHATASE ACTIVITY IN SERUM OF PATIENT WITH SOLITARY ADENOMA OF A PARATHYROID GLAND

	pH <sup>1</sup>			
	4	5	6	9.5
Dec. 4, 1941	7.5	12.5	9.0	78
Dec. 8, 1941	Surgical removal of adenoma			
Dec. 18, 1941	8	15.5	5.5	129
Jan. 13, 1942	2.0	6.0	1.0	
Jan. 15, 1942	1.5	5.0	1.5	56
May 2, 1942		3.0		11

<sup>1</sup> The buffers used in the acid range were acetic acid sodium acetate mixtures while the alkaline buffer was the original King and Armstrong sodium barbital solution.

This study shows that pathological conditions aside from disseminated prostatic carcinoma may produce considerable increases in the acid phosphatase activity in blood.

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# Melanotropic Hormone and Vitiligo

Report of Eleven Cases

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THE PITUITARY gland produces a melanotropic hormone which is responsible for the color of the skin in batrachians. This fact, together with the observation in 1937 of achromias in a number of cases of both hypopituitarism and hyperpituitarism<sup>1</sup> has led to the investigation of the possible effect of a melanotropic hormone on vitiligo.

Successful results were obtained in 1938 by the local application of the purified injectable preparation of the melanotropic hormone in a patient with vitiligo (1) and in 1941 in two other cases of vitiligo treated in the same manner (2).

The purpose of this report is to review these cases to which are added 8 additional patients. The results of therapy were good in 5 of the new cases and no appreciable change was noted in the remaining 3. The beneficial effects consisted of a striking reduction in the area of leucoderma without complete restoration of normal. These patients are still under treatment.

Treatment was started by giving local intradermal injections, 400 frog units twice a week but the changes produced in areas of vitiligo remote from the point of injection showed that the hormone also had a general action at the dosage given.

## CASE REPORTS

**Case 1 J.M.B.**, male, aged 18. Neither the family nor personal history was pertinent. Vitiligo was the chief complaint, the discoloration first appearing over the scrotum about 5 years ago, there being no emotional stress or other cause associated with it. Within 6 months other patches appeared at both wrists and later on the forehead near the hair line (fig 1). Treat-

ment was instituted with the melanotropic hormone by intradermal injections twice a week at the left wrist. After 4 months the areas of discoloration on the forehead began to contract and a year after the institution of therapy had entirely disappeared (fig 2). The other areas of vitiligo changed but little.

**Case 2 A.E.d.M.**, female, aged 33. The family history was unimportant. The patient had been rather fat as a girl, as an adult the weight has been consistently about 80 kg (176 lb). The patient described nervousness and numbness about different parts of the body since she was 12 years old. She was first seen in the clinic late in 1941, (fig 3) complaining of vitiligo over the face, chest and back and some scattered patches over the abdomen and legs. The patches first developed on the back 45 years ago, following this they appeared on the face, and shortly after on the chest, abdomen and legs. The melanotropic hormone was injected intradermally into the frontal patch twice a week for 4 weeks. Because of pain produced by this treatment one injection per week was made into the arm. The patches on the face soon began to disappear following therapy, and they are almost absent at present (fig 4). The largest area of leukoderma on the back is now about one half of its original size and the remaining patches have improved to the same degree.

**Case 3 N.M.**, male, 50 years old. There was no family history of vitiligo. A sister and an aunt have diabetes. The personal history appeared irrelevant. Vitiligo was the chief complaint, discoloration having appeared suddenly about 3 years ago. No mention was made of actual emotional stress or worry. The disease ran a rapid course and within a week was established on the forehead, face and right side of the neck. A month later small patches began to appear on the body and limbs. The patient tried unsuccessfully several topical treatments for 7 months. He then came under our observation and therapy with the melanotropic hormone was instituted consisting of two weekly injections for 6 months, following which the patches on the face apparently improved. After two months the treatment was reduced to a single injection weekly. The patient has been so treated for 2 years and the areas involved have greatly improved, especially the patches on the face (fig 5 and 6).

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<sup>1</sup> The authors mentioned the names of Marañón, Richet, Udel, Netter and Barry, but gave no references.

*Case 4, V.P., female, aged 15.* The family history was unimportant. The patient was of a nervous disposition and reported an increased thirst and sweating, and a sensitivity to cold. She had flat feet. The patient has had vitiligo since the age of 5, when the disease first appeared on both knees with no apparent cause. Following this, it involved the skin over the ankles and finally of the groin by the time she was 8 years old. There has been little progression of the disease in the

patch in the right cervical region. There is no history of emotional shock at the time. The whitish area remained unchanged for 4 years at the end of which time it began to increase in size while new ones appeared on the right side of the nape of the neck. Local intradermal injections of concentrated melanotropic preparation containing 2500 frog units per cc were then given twice a week into the original patch which showed a slight decrease in size after the fourth injection.



FIG. 1, 2. Case 1, aged 18. Vitiligo of 4 years' duration on forehead. Melanotropic hormone twice a week produced improvement within 4 months. Figure 2 made at end of 1 year of therapy.  
FIG. 3, 4. Case 2, aged 33. Vitiligo of 4 years' duration, treatment with melanotropic hormone instituted. Figure 4 shows appearance of patient at present time.  
FIG. 5, 6. Case 3, aged 50. Vitiligo of 3 years' duration. Melanotropic hormone therapy for 2 years. Figure 6 shows appearance of patient at present time.

last 7 years, with the exception of a few single patches on the hands, neck and angles of the mouth. Therapy with melanotropic hormone was instituted nearly 2 years ago, about 120 treatments having been given during this time and consisting chiefly of local intradermal injections twice a week into the skin areas over the knees. These areas have improved in appearance; the small patch on the neck has disappeared and the tint of the few whitish areas still present is less intense. The disease as a whole has ceased to advance.

*Case 5. Y.S., female, age 20.* The patient has a sister, aged 16, with patches of vitiligo. Vitiligo first appeared in Y.S. at the age of 13 in the form of a small

patch in the right cervical region. There is no history of emotional shock at the time. The whitish area remained unchanged for 4 years at the end of which time it began to increase in size while new ones appeared on the right side of the nape of the neck. Local intradermal injections of concentrated melanotropic preparation containing 2500 frog units per cc were then given twice a week into the original patch which showed a slight decrease in size after the fourth injection.

*Case 6. J.M., male, aged 40.* The family and personal history were irrelevant. The patient has always been nervous. Vitiligo has been present for the last 11 years, having first appeared as small patches about the outer corner of both eyes. The skin over the genital and adjacent areas of the abdomen was involved about 5 years later. During the past 3 years vitiligo has

appeared on the lower limbs. At that time treatment with the melanotropic hormone was instituted. A dosage of 2 weekly injections of 400 frog units, 50 injections were thus given into the arm, with intervals of rest between the series. To date there has been no improvement in the existing lesions,

arms, hands, neck, chest and abdomen. Both the onset and the rapid spreading of the disease for the last 3 years have had a background of emotional stress and strain. Treatment has been given for a year, consisting of two weekly injections of the melanophore hormone, 400 frog units each, into the inner aspects of both

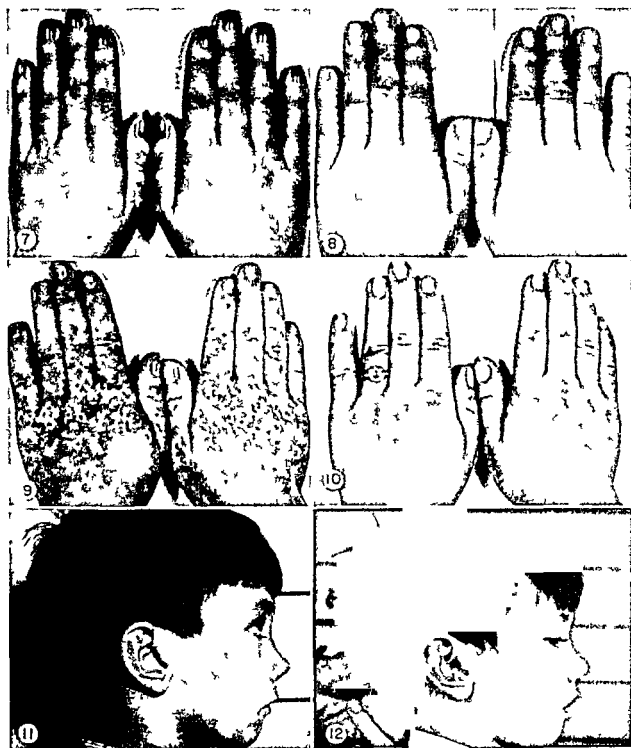


Fig. 7, 8 Hands of 26 year old female with vitiligo of 5 years' duration. Treatment with melanotropic hormone for 2 years. Figure 8 shows hands of patient at present time. Case 7.

Fig. 9, 10 Hands of 16 year old female with vitiligo of 3 months' duration. Disease said to have appeared following severe attack of influenza. Figure 10 shows appearance of hands 4 months after institution of therapy with melanotropic hormone. Case 8.

Fig. 11, 12 Case 11, male, aged 7.5 years. Vitiligo of 2 months' duration. Figure 12 shows appearance after 10 months of treatment with melanotropic hormone. No relapse has occurred 4.5 years after cessation of therapy.

no new patch has appeared during the 10 months of treatment, and the vitiligo already present does not extend.

**Case 7 S.C.**, female, aged 26. The patient gave a personal history of nervousness and irritability. Five years ago she first became aware of small discolored areas developing under the angles of the mouth. Areas of piebald skin subsequently appeared on the fore

arms. The only positive result to be reported is a slight change about the patches on the hands (fig. 7 and 8). The vitiligo is no longer progressing.

**Case 8 M.E.P.**, female, aged 16. The paternal grandmother had vitiligo. The patient sought medical advice because of vitiligo on the hands which was of 3 months' duration. A month after the onset of the disease patches began to appear also on the legs.

There was no connection with emotional factors. The statement was made that the disease followed a severe attack of influenza. Treatment was begun by ionization of the melanotropic hormone through the skin of both hands (3 weekly treatments with a current of 8 milliamperes for one-half hour). Apparent improvement was noted a month later. Therapy was continued for 3 months. The results of treatment in this patient can be seen in figures 9 and 10. Treatment was then discontinued because the patient left this country.

*Case 9. O.C., female, 12 years old.* The personal and family history were irrelevant. Vitiligo of 6 months' duration appeared coincidentally with the secondary sex characteristics. The patient exhibited a large patch on the right side of neck. There was another small area of vitiligo 2 cm. wide at the nape of the neck. Treatment was begun by giving two fresh bovine hypophyses daily and orally. Such treatment was continued for 14 months at the end of which time the cervical patch was approximately one-half of its former size, while the nuchal patch still persisted. Local intradermal injections of the melanotropic hormone were then given, 200 frog units once or twice a week for 20 months, during which time 94 injections were administered in all. Definite improvement was attained. The cervical patch became a small irregular blotch showing a number of tiny circular specks recently pigmented. The nuchal patch disappeared entirely.

*Case 10. R.D. de U., female, aged 24.* The family and personal history were irrelevant. Vitiligo in the past 7 years had spread almost over the entire body. The onset of the disease was associated with an intense emotional shock, its course was slow but increasing. The vitiligo suddenly became worse during the patient's only pregnancy, when it involved formerly healthy regions. The last patches to appear affected the face (chin and around both eyes). The melanotropic hormone was injected intradermally at a dose of 200 frog units twice a week with intervals of rest. The patient had a total of 72 injections in a year; these were always made into the same area of vitiligo (left elbow). A few months after starting therapy pigmentation occurred about the facial patches and continued steadily to the extent of changing the tinge of all of them. The relative effacement of the patches around the left eye can be seen in figures 15 and 16. Little change if any is apparent in the patches on the rest of the body the only difference being that they have become pinkish in hue and thereby offer a less marked contrast with the surrounding normal skin. Moreover the progress of developing vitiligo as a whole has stopped.

*Case 11. D.R., male, aged 7.5 years.* There was history of diphtheria and polyneuritis at 2. The patient exhibited a right-sided facial vitiligo consisting of 5 patches of irregular outline which had appeared 2 months earlier (fig. 11). Intradermal treatment was begun with melanotropic hormone at a dose of 10 frog units twice weekly. There was an almost complete disappearance of the areas 5 months later (fig. 12) and vitiligo had entirely disappeared about 10 months after therapy was begun. At the present time, 4 years after restoration to normal, no relapse has occurred and the color of the skin at the site of original facial patches has remained unaltered.

#### SUMMARY

Treatment of vitiligo with the melanotropic hormone has proved successful as evidenced by the results in 8 of 11 patients thus treated (73%).

In one patient (*case 9*) fresh bovine hypophyses were orally administered; in 9 others a purified extract of the hormone was given either locally or subcutaneously.

The systemic action of such therapeutic measures is shown by the improvement of areas of vitiligo remote from the site of local intradermal injections.

On the basis of investigations on the electrical conveyance of the melanotropic hormone (3), local ionization was successfully tried once in our series (*case 8*).

Improvement has been more rapid and to a greater degree in the patches which have appeared more recently. Satisfactory results, however, have been obtained in cases of vitiligo of 10 years' duration.

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# Therapy of Seminal Inadequacy. II. Use of in Extract of Chorionic Gonadotropin and 'Pituitary Synergist'<sup>1</sup>

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EVANS and his associates (1-5) during the past 12 years have supplied evidence from their studies on the rat in particular that extracts of the anterior pituitary gland enhance the action of chorionic gonadotropin. They considered this enhancement of function a result from the operation of a true synergism and accordingly they have employed the term 'pituitary synergist' to describe this function of the pituitary. This group of workers in 1933 (5) reported that the so-called 'pituitary synergist' had been prepared sufficiently free from the gonad-stimulating and the growth-stimulating principles to render unlikely the possibility that these principles are responsible for this pituitary action.

There has been available commercially during the past year or so a preparation<sup>3</sup> which is said to be a 'balanced' combination of chorionic gonadotropin and the pituitary follicle-stimulating principle or the 'pituitary synergist' of Evans. The manufacturers state that in the preparation of their product the two fractions are obtained separately in highly purified form and that these are combined subsequently in proportions which are judged to yield maximum gonadotropic activity. This proportion is not defined. The unit of potency of this prepara-

tion (to be referred to henceforward as CG+PS) is the 'synergy rat unit' which is described to be 'the minimum total quantity, per rat, which, when injected subcutaneously, in equally divided doses, twice daily for three days into normal immature rats (26-28 days old, Wistar Strain) produces in that time an average ovarian weight five times that of untreated controls.'

Various reports (6-10) have described clinical experimentation with CG+PS in human females. Its preoperative use has been described (6) as having produced stimulation or overstimulation (accessory corpora lutea) in the ovaries of 20 to 23 patients. Despite the fact that this preparation has been described as promoting growth of the seminal epithelium and as stimulating androgenic elaboration by the interstitial tissue of the rat's gonads, no reports of its employment clinically in the therapy of seminal inadequacy have been encountered.

A previous report by members of our group (11) has described the nonoccurrence of significant improvements in the seminal values of 21 males with seminal inadequacy treated with various gonadotropins, including combined therapy with chorionic and pituitary gonadotropins. The present report deals with the results of treating 20 males with seminal inadequacy with CG+PS extract. Six of these 20 males had been treated previously with other gonadotropins, the results of these treatments having been reported in the previous communication.

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<sup>4</sup>Synapoidin, Parke, Davis and Company, Detroit, Michigan.

## METHODS OF STUDY

The impaired seminal function of the 20 males treated was diagnosed during sterility surveys of them and their wives, made because of sterile mating, usually of two or more years' duration. Actual or impending military obligations of the husbands caused two couples, the durations of whose presumed sterility were only  $\frac{1}{2}$  and 1 year, to seek examinations.

In addition to seminal examinations, these males received endocrine and urologic surveys. All had basal metabolic rate determinations and roentgenograms of the sella turcica. Frequently, the levels of 17-ketosteroid excretion were established.

Seminal specimens were studied prior to, during, and after therapy. Adequate continence preceded the collection of specimens. All seminal fluids were collected directly and without the use of condoms. Examinations were made within 15 minutes to 1 hour after ejaculation.

Our seminal studies embraced the following examinations and the acceptance of the following values for normality: volume 4 cc.; immediate motility 80% to 95%; minimal count 60,000,000 per cc. or 240,000,000 for the entire ejaculate; and normal morphology 80% to 95%. For the purpose of analyzing and reporting our data, without the necessity of dealing separately with each of these factors, we have calculated the total number of motile spermatozoa per ejaculate (T.M.S.): the minimal limit for T.M.S. was considered to be 192,000,000. The calculation of a more satisfactory factor, the fertility index (total number of motile spermatozoa with normal morphology) is impossible at present due to the non-availability of suitable supra-vital stains. When significant morphological deviations occurred, and naturally these are not reflected in T.M.S., these are analyzed and reported separately in our data.

With one exception, at least two pretreatment seminal studies were made upon each patient. The total numbers of specimens studied per patient varied from eight to three, the average being five.

Therapeutic schedules embraced the daily intramuscular injection of 30 to 45 synergy units of CG+PS for four to twelve weeks, the average duration of a series of treatments being 5.7 weeks. The average total dosage of CG+PS

per series was 1300 synergy units. Prior to a series of treatment, possible allergy of the patient to the preparation was investigated by intradermal skin tests. Respite from therapy equaled in duration to the period of therapy following each series of injections. A total of 27 series of treatments was given the 20 patients.

The period of observation of our patients with regard to this type of therapy varied from 3 to 18 months. Nine of these patients remain under observation and treatment.

When hypometabolism made advisable the use of thyroid protein or when hygienic errors or constitutional factors existed, seminal alterations incidental to appropriate adjuvant therapy were assessed before the gonadotropic schedules were initiated.

## CLINICAL DATA

The ages of the patients ranged from 24 to 45 years. None of these exhibited signs of pituitary or androgenic deficiency. These were classified into three groups on the basis of physical findings:

*Group I.* Those with normal urogenital findings except for seminal inadequacy (cases 1, 7, 9, 12 and 22 to 29).

*Group II.* Those with partial atrophy of one or both testes but with no evidence of androgenic deficits (cases 13 and 30 to 32).

*Group III.* Those with chronic prostatitis and chronic epididymitis (cases 21 and 33 to 35).

The results of other gonadotropic therapies of patients 1, 7, 9, 12, 13 and 21 have been reported (11).

The pertinent clinical data of these 20 patients, including seminal assessments on the basis of total motile spermatozoa in the ejaculates, are summarized in table 1. Graphic presentation of the seminal findings and therapy of these patients in figures 1 to 6 provides data upon each seminal examination with regard to volume, morphology, immediate motility and number of spermatozoa per cc.

Data from seminal examinations made more than 18 days after the initiation of therapy and not more than 10 days following its cessation were considered treatment values. Those secured more than 10 days after the cessation of therapy and not more than 30 days after its cessation were considered immediate post-

TABLE 1 SUMMARY OF CLINICAL DATA ON 20 PATIENTS WITH SEMINAL INADEQUACY

Case number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pre treatment Values			Average Treatment Values		Average Values Immediate Post treatment		Average Values Delayed Post treatment		Follow up	
				Number, Sem Exams	Total Motile Sperms, Millions	Total Dosage CG+PS 'Synergy Units'	Number, Sem Exams	Total Motile Sperms, Millions	Number, Sem Exams	Total Motile Sperms, Millions	Number, Sem Exams	Total Motile Sperms, Millions	Wife Became Pregnant	Further Studies and If
Group I														
1	43	3½		2	2 6	2,670	3	T F C <sup>1</sup>	1	2 5	2	11 1	No	Now
7	39	4		2	T F C	1,050	1	T F C					No	No
2	24	½		2	T F C	1,260	1	aspermia	1	aspermia			No	Now
						1,260								
13	32	5		3	aspermia	1,890	1	aspermia			1	aspermia	No	No
9	32	5		2	5 6	840	1	0 1			1	1 0	No	No
2	31	2		1	148 7½	840	2	305 0*	1	92 0	1	48 4	Yes	
						840								
4	27	1		3	37 7	1,260	2	95 1					No	Now
15	30	14		5	70 8	1,260					1	48 9	No	No
16	29	2		2	96 0	1,470	2	24 4			1	26 0	No	No
17	30	4		2	7 2	1,260	2	34 4					No	Now
18	32	5		2	4 3	1,260	2	1 9			2	2 3	No	No
						1,260								
19	34	2		2	434 0½	1,260	1	463 0½	1	59 5			No	Now
						1,260								
Group II														
13	30	2	Right testis ½ normal size, left somewhat hypertrophied	2	69 1	840	2	127 5			1	62 0	No	Now
						1,260								
30	45	2	Moderate atrophy of both testes	3	2 1	1,260	2	2 0			1	2 7	No	Now
						1,890								
31	28	2	Right testis in inguinal canal, left somewhat hypertrophied	2	5 6	1,260	2	0 08			1	1 3	No	Now
						1,260								
32	32	2	Failure of descent of right testis, left somewhat hypertrophied	2	11 4	1,260	1	11 8					No	Now
Group III														
21	30	8	Chronic epididymitis	4	31 7	1,260					1	5 9	No	No
33	31	3	Chronic prostatitis	3	27 1	840	1	75 0			1	28 8	No	No
34	30	2	Chronic epididymitis	2	aspermia	1,050	1	T F C					No	No
35	45	12	Chronic epididymitis	2	T F C	1,680	2	T F C					No	No

<sup>1</sup> T F C indicates too few spermatozoa to count<sup>2</sup> Indicate instances in which the pathological seminal finding, i.e., decreased percentage of normal morphology, which occasioned therapy is not reflected in the formula T M S (total motile spermatozoa)<sup>3</sup> Corresponding pretreatment and treatment values for normal morphology in case 12 are 66% and 53%<sup>4</sup> Corresponding pretreatment and treatment values for normal morphology in case 29 are 68% and 62%

treatment values Those which were secured more than 30 days after the conclusion of therapy were considered delayed post-treatment values

## DISCUSSION

Reference to table 1, which is concerned with data on seminal values expressed in terms of total motile spermatozoa, indicates no con-

sistent trend in the seminal values during treatment: of the 18 patients, concerning whom these values were available, those of eight were increased and those of five were decreased by varying amounts over pretreatment ones, while those of the remaining five were essentially not changed The alterations observed in the treatment values of seven of the eight patients whose values were increased were generally small, the



factors for these increased treatment values in terms of the pretreatment ones were in order of magnitude: 4.77, 2.76, 2.52, 2.05, 1.84, 1.06 and 1.03. The only instance in which the T.M.S. rose sufficiently during therapy to warrant the assumption that the fertility of the patient had been altered significantly was that of the patient

eight patients were decreased over the pretreatment ones, those of three were increased varying amounts while those of one patient were essentially unchanged. Delayed post-treatment values are available for four of the eight patients whose seminal values were increased during treatment: these values of three were decreased

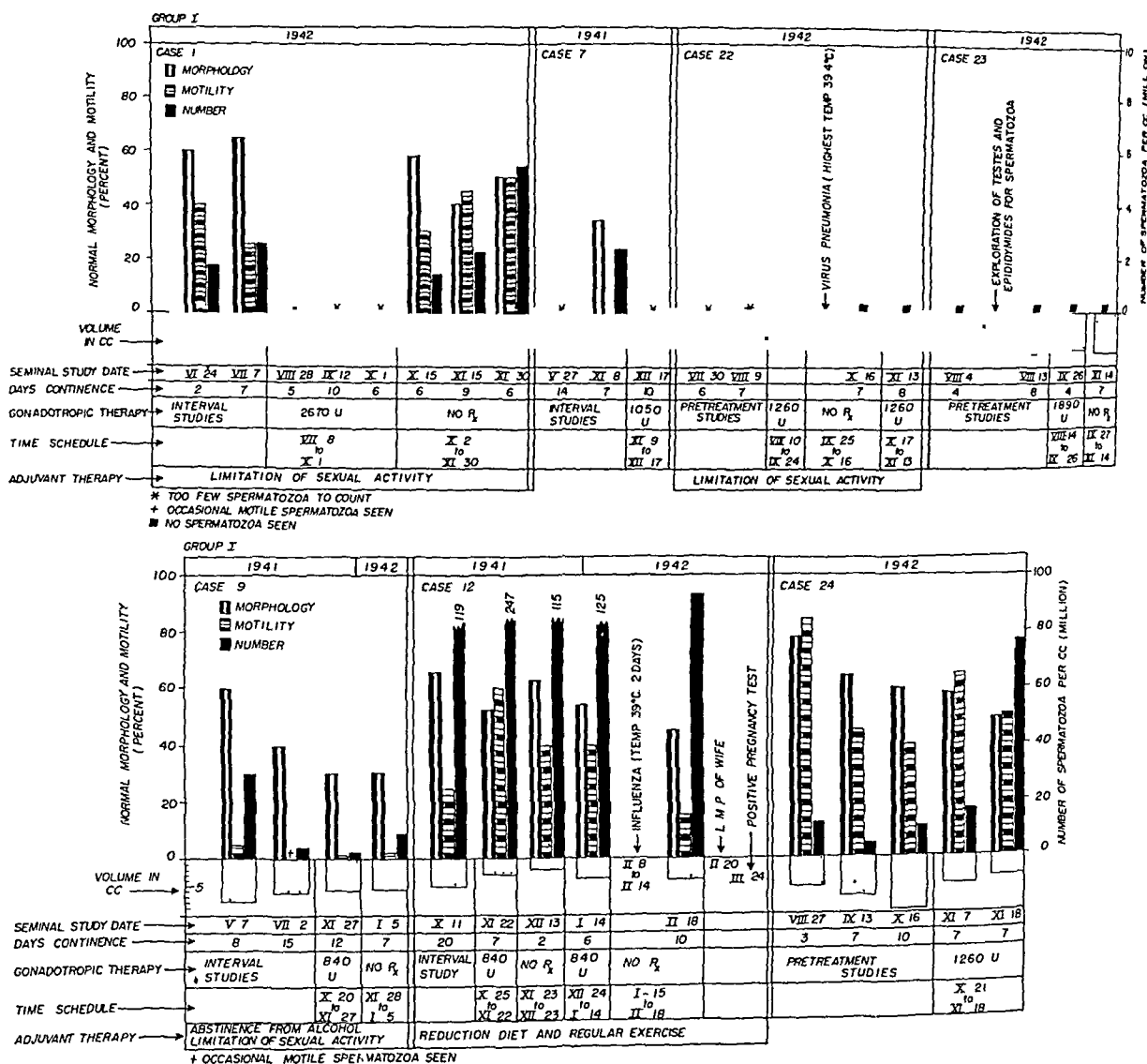


FIG 1 Clinical data on cases 1, 7, 22 and 23.

FIG 2 Clinical data on cases 9, 12 and 24.

in case 12, whose wife became pregnant despite a temporally associated marked drop in T.M.S. following discontinuation of therapy (figure 2).

Data, however, with regard to the end results of therapy, as judged by delayed post-treatment seminal studies, show a definite trend toward seminal values which are less than the pretreatment ones. Of the 12 patients concerning whom these data were available, values of

while those of one were increased very slightly (T.M.S. 27.1 to T.M.S. 28.8).

No correlation was established between the physical status of the patients and their responses to therapy. Despite the fact that the 12 patients of group I were considered more likely to respond to therapy because of their non possession of demonstrable urogenital pathology than the four patients of group II and the four

patients of group III, the observed improvements in seminal values did not bear out this assumption: four of the 12 patients (33%) of group I exhibited increased treatment values; two of the four patients (50%) of group II; and

strate that therapy consistently improved any particular factor studied in the seminal examination: either volume, number of spermatozoa, morphology or immediate motility. Furthermore, there is no apparent correlation between

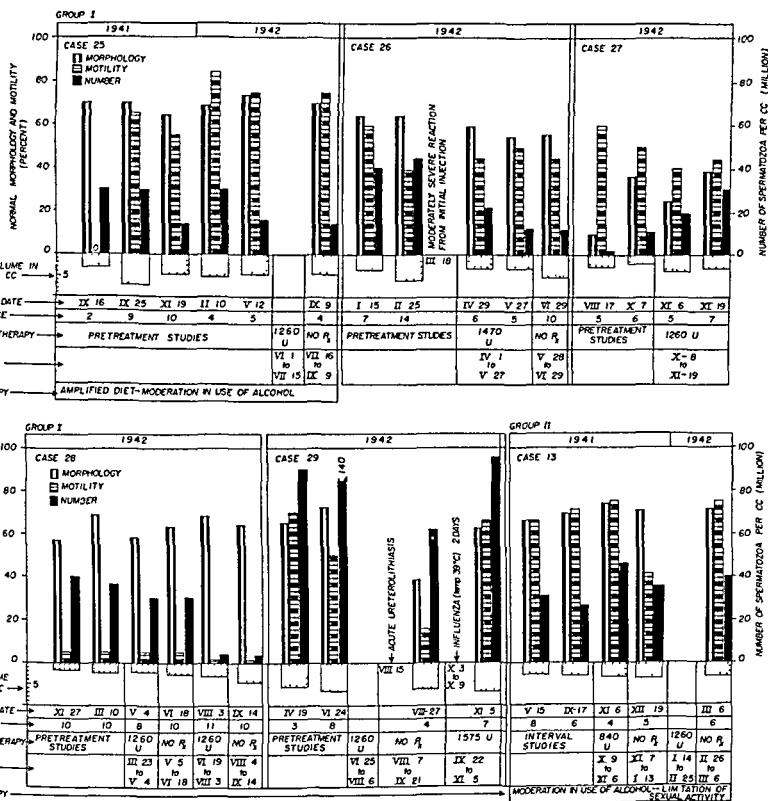


FIG 3 Clinical data on cases 25, 26 and 27

FIG 4 Clinical data on cases 28, 29 and 13

two of the four patients (50%) of group III. Figures 1 to 6 bear testimony to the fluctuations which occur spontaneously in the seminal values of the same individual prior to therapy and during therapy. These were frequently of essentially the same order under both conditions, a fact which renders recognition of significant improvements difficult.

Further analyses of our data fail to demon-

strate the degree of seminal impairment and the effectiveness of therapy.

The statement made in our previous report (11) that none of the patients who received gonadotropic therapy permitted a definite diagnosis of hypogonadotropic pituitary failure applies equally to the patients included in this report. Until adequate clinical methods are devised for quantifying levels of pituitary function

and degrees of gonadal responsiveness, therapeutic testing of patients with gonadal deficiencies with gonadotropic extracts doubtlessly will continue to be considered expedient.

In view of a recent report of the occurrence of a severe anaphylactic reaction to CP + PS (12), comment on the tolerance of our patients to

tion, there was a temperature of  $38.8^{\circ}\text{C}$ . and pain and swelling at the site of injection. One week later another injection was given and this was followed promptly by severe local and constitutional reactions—temperature of  $40.0^{\circ}\text{C}$ , chills and aching joints. Another patient had a severe local reaction to his first injection, which

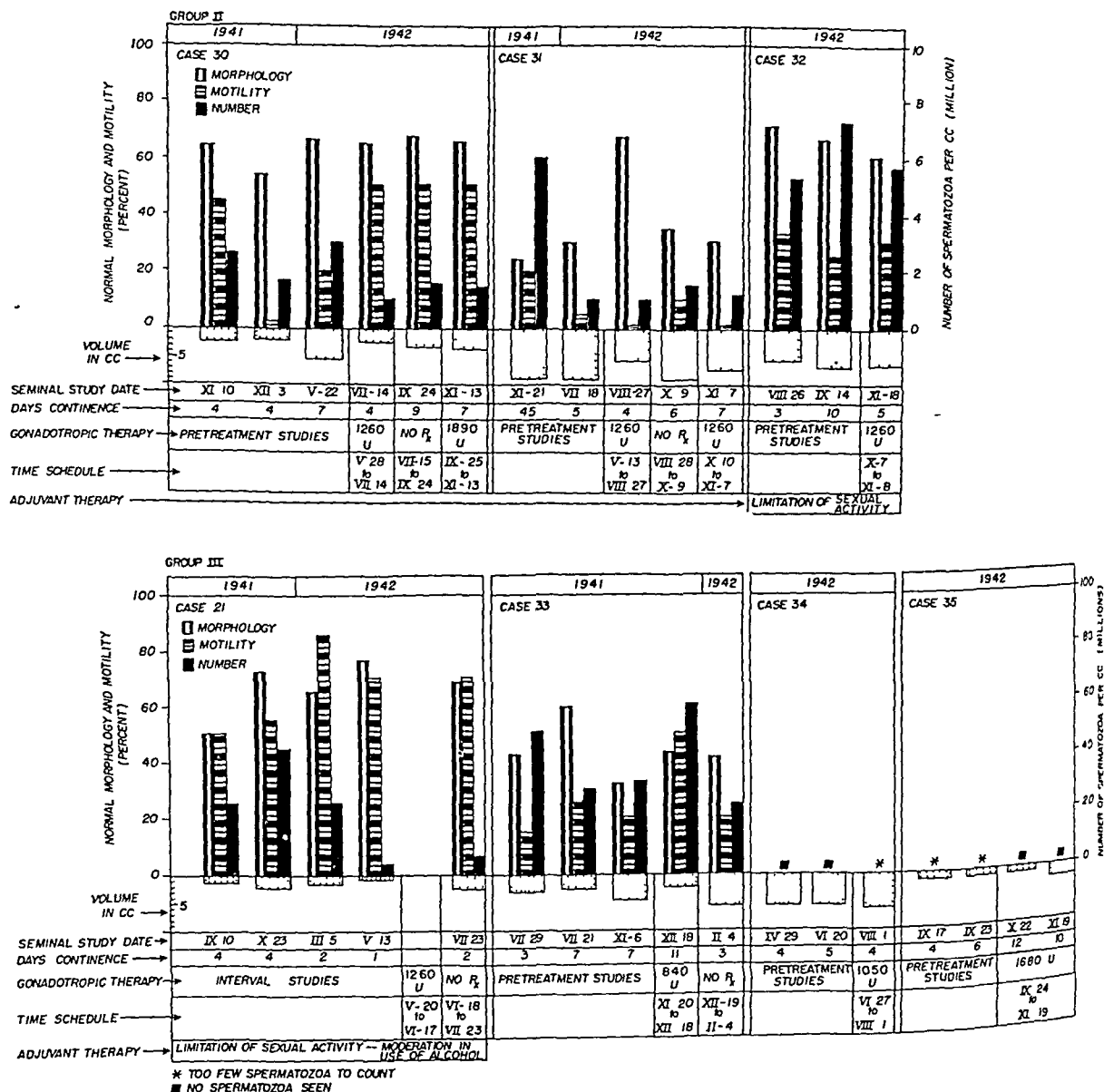


FIG. 5. Clinical data on cases 30, 31 and 32.

FIG. 6. Clinical data on cases 21, 33, 34 and 35.

this preparation seems advisable. Despite the fact that no patient was treated who was not negative to skin tests with the preparation prior to each intended series of injections, one of our patients (not included in this series) had severe reactions which prevented continuation of therapy. Three hours after his first injection

was given during a time when active immunizations preparatory to military service were being carried out. Later, when these were completed, he was able to proceed with CG+P injections without any untoward reactions.

In conclusion, we are of the opinion that, based on our analyses of data been confined solely to pre

treatment and treatment seminal values, we might have considered these data to justify the hope that an occasional patient might expect desirable effects on his fertility from this type of therapy. Our studies, however, of delayed post-treatment values, initiated as they were to explore the possibility that therapy with CG+PS might exert delayed benefits, have nullified any real hopes for therapeutic salvage. These indicate not only that the few apparent improvements in seminal values which occur concurrently with treatment are evanescent and give way to values often lower than pretreatment ones when treatment has been discontinued but also that seminal values not improved during therapy often are depressed further in conjunction with this therapy. The cause of these apparent inverse responses has not been determined. Since these are not relatable to the higher dosage schedules employed or to the more protracted treatments given, it does not follow necessarily that these are due to antibody phenomena. This possibility, however, must be considered.

#### SUMMARY

Twenty male members of childless couples, with seminal inadequacy, whose ages (when first seen) ranged from 24 to 45 years and the duration of whose sterile matings ranged from  $\frac{1}{2}$  to 14 years, were investigated and treated with an extract containing chorionic gonadotropin and pituitary synergist.

Twelve of these patients presented no physical signs of andrologic disease, four had partial atrophy of one or both testes, and four gave evidence of chronic epididymitis and/or prostatitis. None presented symptoms or signs of pituitary disease or androgenic deficiency.

Therapeutic schedules embraced the daily

intramuscular injection of 30 to 45 'synergy units' of the extract for four to twelve weeks, the average duration of a series of treatment being 5.7 weeks and the average series dosage being 1300 units. In all 27 series of injections were given.

Seminal values during therapy manifested no significant trend: in 8 of 18 patients these were elevated varying degrees while those of five patients were decreased. The fertility of one patient was judged to have been definitely enhanced in that his wife became pregnant.

Delayed post-treatment values, however, showed a definite trend (in 8 of 12 patients or 75%) toward levels lower than initial pre-treatment ones. Antibody phenomena were considered with regard to explaining these inverse responses.

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# Breast Hypertrophy in the Male

## Report of Two Cases of Pseudogynecomastia with Surgical Reconstruction

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IN THE LAST two years mobilization for military and industrial purposes has brought many young people into close proximity in camps, barracks and factories where there is little personal privacy. As a result, certain physical abnormalities which are easily concealed in civilian life, can no longer be hidden. Among such malformations gynecomastia, is of relative frequent occurrence, often producing pronounced psychic depression.

Gynecomastia, a term applied to hypertrophy of the male breast, may present itself in two forms, true gynecomastia and pseudogynecomastia. The former is a tumor-like condition frequently due to proliferation of the ducts and periductal tissue. It is usually unilateral and of limited proportions and does not call for surgical intervention.

Many workers in this field have found true gynecomastia to be related to disturbances in the testes, pituitary gland and the adrenal cortex (1). It appears most frequently as a small, often painful, glandular swelling adherent to the nipple.

Prior to recent endocrinologic progress, the etiologic factors underlying this condition were more or less the subject of speculation. Recent work on the endocrines, however, shows that the female hormones are present in both males and females and that there may be an overbalance of female hormones in some males, and *vice versa* (2). True gynecomastia can be attributed to this hormonal imbalance and resulting sexual deficiencies.

Pseudogynecomastia is usually bilateral and manifests itself as an adiposis of the breast,

which is soft, painless and may reach large proportions. Here to the normal glandular elements of the breast is added fatty hyperplasia. Hormonal therapy may have some influence on this adiposis, but it is rarely conquered thereby, and the patient suffers from extreme sensitivity, often a pronounced psychic depression, because of the presence of mammary hypertrophy. This malformation can often be greatly improved by surgery.

### CASE HISTORIES

The following case histories are characteristic of the type of patient with pseudogynecomastia who is greatly benefited by surgery.

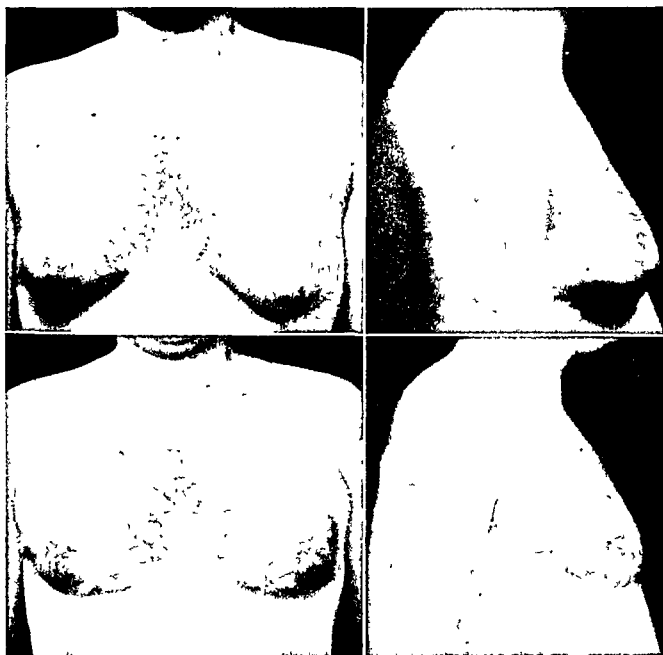
*Case 1.* (fig. 1). A male, age 30, was first seen in November, 1939. The patient had suffered from pronounced mental depression since the age of 15, avoided the companionship of other youths and taking no part in sports of any kind. Even in the hottest summer weather he would insist on wearing a vest. His parents were completely ignorant of the factors underlying his abnormal mental state.

On physical examination no abnormalities were revealed except for local findings. At the age of 15 he had had a fibrocystic osteitis of the right arm, treated by roentgen-ray, which had left a conspicuous bony scar. The general appearance was that of a normally developed male, considerably overweight because of sedentary habits. His manner was shy and retiring, but he was able to conduct normal everyday business activities. The patient had a bilateral fatty hyperplasia of the breasts, which had the appearance of female breasts at puberty. They were slightly pendulous, soft, with a deep submammary fold. The areolae were conspicuously large. No tumor-like masses could be palpated. There was no secretion from the ducts. The other sex characteristics, including the distribution of body hair and the development of the sex organs were normal. During the previous 6 months he had been receiving treatment by a competent endocrinologist without result.

The patient admitted extreme sensitiveness about mammary development which made him secretive about it, even with his closest relatives. Reconstruction surgery was advised and accepted without hesitation. The improvement following surgery was most gratifying. The entire mental attitude of the patient underwent a marked transformation for the better and attained a complete mental and social rehabilitation. The pathologist's report of the mammary tissue

and about the size of normal mammae in a girl of 14. The areolae were enlarged. The patient appeared sexually normal.

In spite of the relatively limited malformation of the breasts, he exhibited great sensitiveness and reluctance to undress in the presence of others. He never took part in sports requiring removal of clothing and never went in swimming. The latter fact, he claimed, was the chief reason he sought medical advice. In-



became indiscernible.

showed the hypertrophy to be due to adipose tissue, the breast stroma was normal with an average number of normal-appearing ducts and no acinar cells. The appearance of the specimen differed considerably from that of a true gynecomastia or fibroadenoma, in which there is proliferation or hypertrophy of the pericanalicular connective tissue with some hyperplasia of the duct epithelium.

Case 2, was a male, age 26, first examined in 1940. There was a slight overdevelopment of both breasts, which were of rather firm consistency. No tumor masses could be palpated and there was no secretion from the ducts. The breasts were moderately enlarged

and the familial history revealed pronounced breast hypertrophy in the mother and sister of the patient. For a number of months he had been undergoing regular endocrinologic treatment without improvement. Because of the moderate enlargement, surgery was not urged but was finally performed at the urgent request of the patient.

The microscopic examination of the removed breast tissue showed "fibrotic breast containing ductules with regular cuboidal epithelium, in the resting phase. Diagnosis: fibrotic breast tissue without significant changes in the epithelium." The mental improvement of the patient following surgery was gratifying.

### *Surgical Procedure*

The purpose of reconstructive surgery in these cases is to reduce the hypertrophy of the

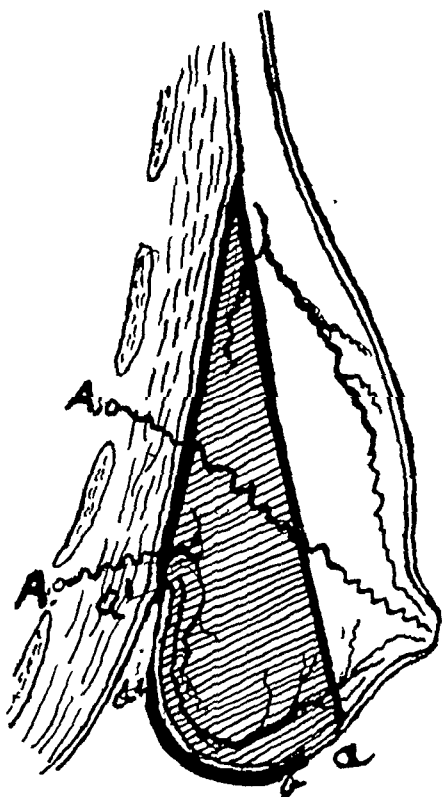


FIG. 2. Diagram illustrating the wedge-shaped excision from posterior aspect of mammary gland. a-a', forms the base of the glandular wedge; b-b', crescent-shaped excision of skin; A, branches of intercostal arteries which are easily retracted on the pectoral fascia from posterior surface of breast.

breast in the antero-posterior diameter without disturbing the nipple (fig. 2).

The incision is made in the submammary fold to conceal conspicuous scarring. The approach through the posterior aspect of the mammary gland permits avoidance of the main vascular pedicles of the breast, the internal mammary artery and the lateral thoracic artery, on which the blood supply of the nipple and skin depends. This eliminates the problem of bleeding and allows easy separation of the mammary gland from the pectoral fascia. The only blood vessels encountered are the branches of the intercostals, which are retracted from the gland without difficulty as they run along the pectoral fascia (fig. 2, A).

A wedge-shaped segment of mammary tissue is excised along the entire height and width of the breast, leaving a section of the gland attached to the nipple. The amount of tissue to be removed depends on the extent of hypertrophy. Excess skin along the submammary fold is excised in a crescent shape (fig. 2, b-b'). Following careful hemostasis, the mammary gland is attached to the pectoral fascia. The incision is closed following some skin adjustment to equalize the skin flaps.

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# Structure of the Human Anterior Pituitary Gland after Administration of Estrogenic Hormones

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IN THE PAST few years, there has been a large amount of experimental work on the effect of estrogenic and other steroid hormones on the anterior pituitary gland of several species of animals. The literature has been reviewed by Severinghaus (1, 2) and Zondek (3). His work has emphasized the markedly labile activity of the anterior pituitary, and has clarified some of its numerous interrelationships with the other endocrine organs. It has also offered some clue to the genesis of 'adenomata' of the anterior lobe. However, with the exception of Zondek's (4) paper, there are no reports on similar experimental work in man. This study was undertaken to determine the effects, if any, of different amounts of intramuscularly administered estrogens on the pituitary glands of men and women.

## METHODS

Thirteen patients in advanced stages of chronic diseases were selected who had no obvious clinical endocrine disorder. These included cases with cardiac disease, pulmonary tuberculosis, malignant lymphomatosis and organic nervous disorders. Table 1 shows the age, sex, clinical diagnoses and the dosage schedule. Estrone<sup>1</sup> was used in doses of 20,000 I U (2 mg of estrone) and estradiol benzoate<sup>2</sup> in doses of 66 mg or 10,000 R U. The injections were made at varying intervals, depending upon the condition of the patient. A complete autopsy was performed in most instances. In each case,

<sup>1</sup>Received for publication February 12 1943  
<sup>2</sup>The estrone (Ammiotin) was supplied by E. R. Squibb and Sons, N. Y.  
chir was supplied by

the pituitary gland was weighed after fixation in Orth's fluid. The gland was sectioned sagittally at several levels. The sections were stained with hematoxylin-eosin and with Mallory's triple connective tissue stain preceded by hematoxylin. Cell counts of the anterior lobe were not made. Routine hematoxylin-eosin preparations were made of the other organs.

## FINDINGS

*Case 1, male, aged 19 yr, Hodgkin's disease.* *Testes:* There was no spermatogenesis. Spermatogonia were present. Leydig cells appeared to be increased. *Pituitary:* The basophils were increased to about 20 per cent, the majority being ripe, with many bizarre forms. The transition basophils were increased in number, some showing hydropic and a few colloid change. The acidophils were normal in appearance. There was some hyperplasia but its relation to the administered estrogen was in doubt due to the testicular changes.

*Case 2, male, age 21, pulmonary tuberculosis.* *Testes:* There was some decrease in spermatogenesis. A few spermatids and rare spermatozoa were present. The Leydig cells seemed to be slightly increased. *Pituitary:* There was an average number of basophils but the nuclei were enlarged and vesicular. The number of transition forms were increased, with a few at the hydropic stage. The acidophils were increased in number, their nuclei enlarged and vesicular. There was a moderate degree of granule loss up to the hydropic stage. There was a minute nodule of transition acidophils (fig. 3). The capillaries were compressed. There was hyperplasia involving largely the acidophils.

*Case 3, male, age 22, pulmonary tuberculosis.* *Testes:* There was active spermatogenesis. The Leydig cells were decreased. *Liver:* There was slight amyloidosis. *Pituitary:* The basophils were increased to about 30 per cent and there were large numbers of swollen, watery transition basophils with swollen nuclei (fig. 1). Basophils of the castration cell type with pyknotic nuclei were also present. The acidophils were increased in number with marked pleomorphism, granule loss and nuclear hypertrophy. Many binucleated chromophils were present. The capillaries were compressed. There was a marked hyperplasia, involving acidophils and basophils, largely the latter.



Case 4, male, age 23, pulmonary tuberculosis. *Testes.* Spermatogenesis was arrested at spermatogonia stage and the Leydig cells appeared to be increased. *Pituitary.* The basophils were increased to about 20 per cent, the majority being ripe with slight increase in transition forms. The acidophils were increased, with only a few atypical forms. A minute nodule of transition basophils was present in the lateral portion of the anterior lobe. There was an increase in the number of ripe chromophils.

Case 5, male, age 23, Hodgkin's disease. *Testes.* Spermatogenesis was arrested at spermatocyte stage.

was a slight increase in the basophils; the transition forms were increased in number with few at the dropic stage. The acidophils were increased, as were the transition forms with several minute areas of simple hyperplasia near the pars intermedia. There was a microscopic nodule of polygonal vacuolated transition basophils and a minute area containing atypical, transition acidophils appearing to be localized simple hyperplasia. There was a small focus of simple hyperplasia consisting of small transition basophils. There was a generalized mild hyperplasia with several localized foci.

TABLE 1. STRUCTURE OF HUMAN ANTERIOR PITUITARY GLAND FOLLOWING ESTROGEN ADMINISTRATION

Case No.	Age	Sex	Diagnosis	Total Dose of Estrogen <sup>1</sup>	Period of Treatment	Interval after Last Dose	Weight of Pituitary	Structure of Anterior Pituitary
1	yr. 19	M	Hodgkin's disease	260,000 I.U. (26 mg. estrone)	days 25	days 3	mg. 615 <sup>2</sup>	Appeared normal
2	21	M	Pulmonary tuberculosis	120,000 I.U. (12 mg. estrone)	27	4	475 <sup>2</sup>	Mild hyperplasia
3	22	M	Pulmonary tuberculosis	240,000 I.U. (24 mg. estrone)	68	34	450 <sup>2</sup>	Marked hyperplasia
4	23	M	Pulmonary tuberculosis	60,000 I.U. (6 mg. estrone)	8	83	490 <sup>2</sup>	Appeared normal
5	23	M	Hodgkin's disease	100,000 I.U. (10 mg. estrone)	9	2	320 <sup>2</sup>	Mild hyperplasia
6	24	M	Pulmonary tuberculosis	180,000 I.U. (18 mg. estrone)	12	2	510 <sup>2</sup>	Mild hyperplasia
7	34	M	Lymphosarcoma	20,000 I.U. (2 mg. estrone)	1		450	Appeared normal
8	60	M	Multiple sclerosis	6.6 mg. estrad. benz. (40,000 R.U.)	9	3	575	Marked hyperplasia
9	65	M	Amyotrophic lateral sclerosis	43.8 mg. estrad. benz. (264,000 R.U.)	294	1	410	Marked hyperplasia
10	25	F	Rheumatic heart dis.	200,000 I.U. (20 mg. estrone)	31		430 <sup>2</sup>	Mild hyperplasia
11	27	F	Rheumatic heart dis.	220,000 I.U. (22 mg. estrone)	29	3	685	Appeared normal
12	32	F	Pulmonary tuberculosis	40,000 I.U. (4 mg. estrone)	4	3	635 <sup>2</sup>	Appeared normal
13	32	F	Pulmonary tuberculosis	11.6 mg. estrad. benz. (70,000 R.U.)	9	1	720	Marked hyperplasia

<sup>1</sup> 10,000 I.U. of estrone (Amniotin)  $\approx$  1 mg. of estrone; 1.667 mg. of estradiol benzoate (Progynon-B)  $\approx$  10,000 R.U. (Alte Doisy). The estrone unit is not the same as the estradiol benzoate unit. One gm. of estrone = 10,000 I.U. One gm. of estradiol benzoate = 10,000 I.B.U. On biologic test, estradiol benzoate is 6 times as effective as estrone, mg. for mg.

<sup>2</sup> Denotes slight damage to posterior lobe in removal. Hence the true weight is slightly greater.

Leydig cells were present in average numbers. *Pituitary.* The basophils were present in average numbers, the majority of which were ripe. A few transition forms were observed. The acidophils were increased in number, the majority of which were ripe, but the transition forms were increased with the appearance of growth in places. There was one large sheet of hydropic transition acidophils. A moderate number of chromophils of the castration cell form of both types were present. A mild hyperplasia existed chiefly involving the acidophils.

Case 6, male, age 24, pulmonary tuberculosis. *Testes.* Spermatogenesis arrested at spermatocyte stage, with a few spermatids present. The Leydig cells appeared to be average in number. *Pituitary.* There

Case 7, male, age 34, lymphosarcoma. *Testes.* Spermatogenesis was arrested at the spermatogonia stage. The Leydig cells seemed to be slightly increased. *Pituitary.* The basophils were increased to about 20 per cent and there were small adenomatoid nodules of ripe cells, many of which were bizarre in form. The acidophils showed a moderate degree of pleomorphism. Numerous hydropic, degranulated cells with large vesicular nuclei were seen; these probably were of acidophilic and basophilic origin. Some hyperplasia was noted.

Case 8, male, age 60, multiple sclerosis. *Testes.* There was a very slight decrease in spermatogenesis. The Leydig cells present were average in number. *Pituitary.* The basophils, average in number, had

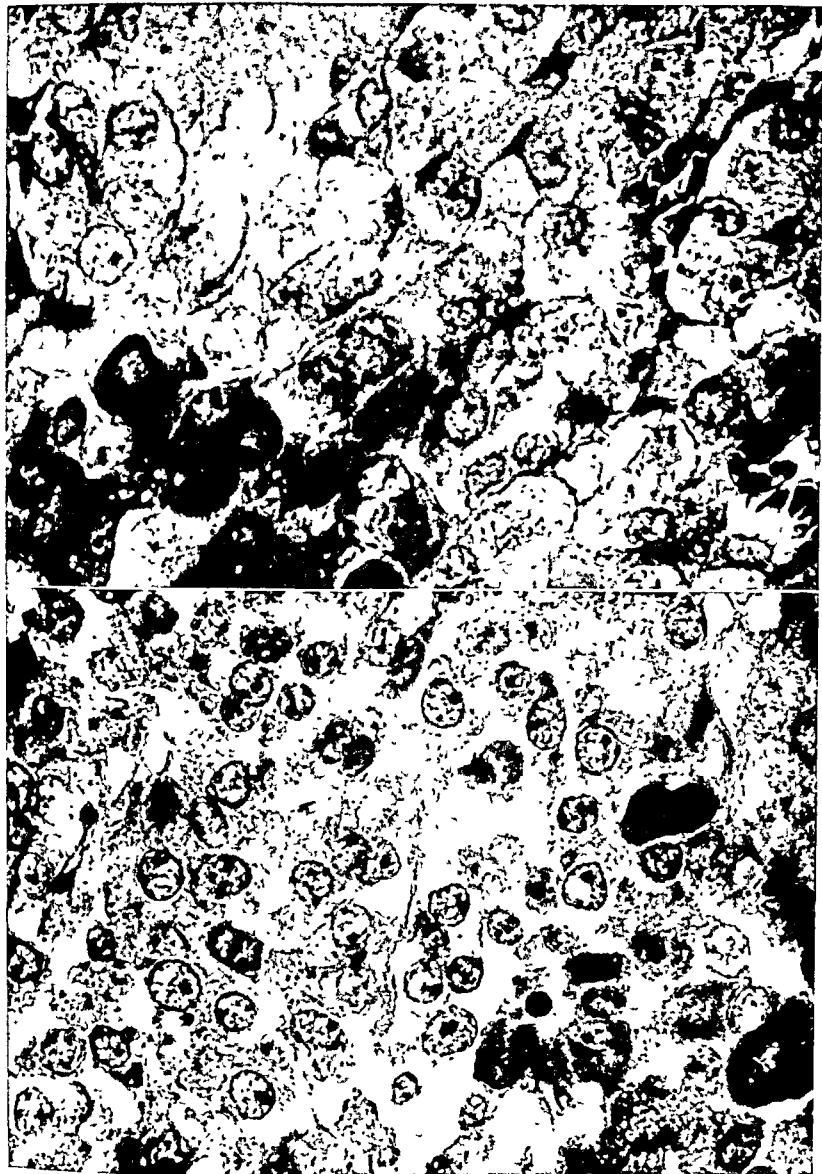


FIG 1 (*upper*). Anterior region of anterior lobe, case 3 The ripe basophils appear dark. The transition basophils are droptic and swollen and closely approximated Nuclei are enlarged and vesicular. No acidophils shown in microphotograph 550

FIG 2 (*lower*). Posterior region of anterior lobe, case 13 The ripe acidophils appear dark. Note the syncytial appearance the transition acidophils, with large vesicular nuclei, prominent nucleoli and watery cytoplasm containing lightly staining inules No basophils shown in microphotograph  $\times 650$ .

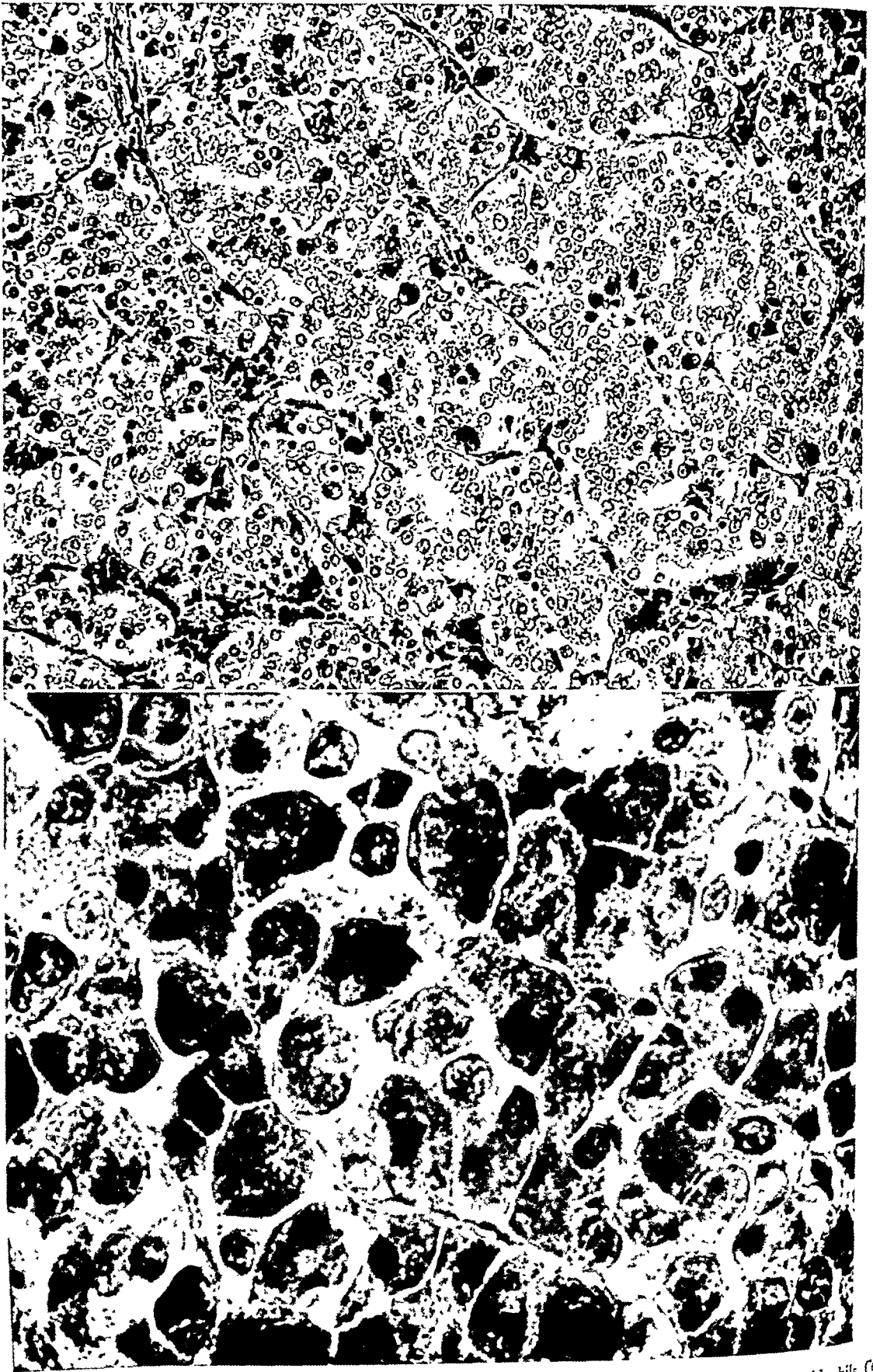


FIG. 3 (*upper*). Posterior region of anterior lobe, *case 2*. Localized area of hyperplasia of transition acidophils  $C_e$  arranged in anastomosing cords.  $\times 160$ .

FIG. 4 (*lower*). Anterior lobe, *case 10*. Ripe acidophils. Note solid chromatin of nuclei of normal size. Granules are large and stain deeply. Compare with degranulated acidophils in figure 2.  $\times 650$ .

ged vesicular nuclei. The number of transition forms increased and colloid changes were observed in a small proportion, one mitotic figure occurred. There were several minute areas of simple hyperplasia of ripe transition basophils. The acidophils were increased in number and had enlarged and vesicular nuclei, the granule loss was moderate and there were numerous hydropic cells. Numerous small areas of simple hyperplasia of ripe or degranulated acidophils were observed. There was compression of the capillary bed and mild hyperplasia chiefly involving the acidophils.

*Case 9, male, age 65, amyotrophic lateral sclerosis of the brain and hypophysis only were examined. Pituitary.* There was a slight increase in the number of acidophils and of the transition forms up to the hydropic stage. The nuclei of the transition cells were very large and vesicular or small and dark (castration type). There were several foci of syncytial transition acidophils. Many of the basophils invading the posterior lobe showed granule dispersion with hydropic cytoplasm. The acidophils and transition forms were increased. There was an area of simple localized hyperplasia of transition acidophils adjacent to the intermedia. A small nodule of hydropic, transition type, probably acidophilic in origin, was observed at the anterior pole. The capillary bed was compressed, marked general hyperplasia involving anterior lobe cells and posterior lobe basophils was apparent with localized areas of hyperplasia of acidophils.

*Case 10, female, age 25, rheumatic heart disease, ovaries and uterus. No abnormalities. Endometrium, interval stage. Pituitary.* The basophils were average in number with many atypical ripe cells. A few showed granule dispersion, some approaching the colloid type. There was one minute nodule composed of atypical transition basophils. The acidophils were increased in number, the majority being ripe (fig. 4). There were many transition forms including a large sheet of hydropic transition acidophils in the region of the pars intermedia. There was a minute nodule of atypical transition acidophils adjacent to Rathke's cleft. Scattered castration cells with dark nuclei were observed. There was a mild hyperplasia chiefly affecting the acidophils and several minute foci of localized simple hyperplasia of acidophils and basophils.

*Case 11, female, age 27, rheumatic heart disease, ovaries and uterus. No abnormalities. Endometrium, interval stage. Pituitary.* The basophils were average in number and of normal morphology. The acidophils were increased in number, but were of normal morphology. Four areas of nodular hyperplasia were present: 1), 2 mm in width composed of cells, chromoblasts, acidophils and basophils; 2),  $\frac{1}{2}$  mm in width containing transition and ripe basophils; 3),  $\frac{1}{2}$  mm in width consisting of transition and ripe acidophils and a small nodule of transition and ripe basophils. There was no diffuse hyperplasia.

*Case 12, female, age 32, pulmonary tuberculosis*

*Ovaries and uterus.* No abnormalities were observed. *Thyroid.* There were areas of atrophy and hyperplasia. *Liver.* There was evidence of very slight amyloidosis. *Pituitary.* The basophils were average in number, the majority of which were ripe. A few transition forms were observed. The acidophils were increased in number and the majority were ripe and had large vesicular nuclei. More than half of these had large nuclei and scanty, granular cytoplasm. There was only slight granule loss from the many huge, ripe acidophils, some with 2 or 3 nuclei. There was a mild hyperplasia affecting the acidophils.

*Case 13, female, age 32, pulmonary tuberculosis.* Only pituitary examined. The basophils were increased to about 15 per cent. Small nodules of adenomatoid hyperplasia occurred. The majority of the basophils were ripe, but there were numerous transition forms, some of which were at the hydropic stage. There was a marked increase in the number of acidophils with enlarged nuclei which were either vesicular or hyperchromatic. There was a marked granule loss (fig. 2). Several small areas of simple localized hyperplasia of atypical transition acidophils occurred, one appearing almost neoplastic. In the anterior region there was a microscopic nodule of atypical transition acidophils. The capillary bed was compressed. Hyperplasia was marked and largely involved the acidophils, minute areas of localized hyperplasia were observed.

# GENERAL DISCUSSION

The anterior pituitary can respond to a given agent by hyperplasia of a normal gland, or involution of a hyperplastic one.

With hyperplasia, a new formation of chromophils from chromophobes is observed. The nuclei enlarge, with or without changes in the chromatin content, and they may also divide amitotically to form binucleated or multinucleated cells. Pyknosis may occur as a manifestation of cell exhaustion. The cytoplasm may show granule loss or dispersion, with either a watery, vacuolated or colloid ground substance remaining. Changes in cell shape and thinning of the capillary bed are due to altered pressure relationships, resulting from cellular hyperplasia and hypertrophy. Localized areas of hyperplasia may occur, and these may be well circumscribed, and take the form of the so-called adenoma. This type of hyperplasia is found in the human anterior pituitary in pregnancy, and in the experimental animal after thyroidectomy or estrogen administration. I have observed the same type of response in several eunuchoid male individuals. A complex morphologic picture can be produced in the an-

terior pituitary when, as frequently occurs, more than one agent acts upon it. The confusion in the literature regarding pituitary morphology in different conditions can thus be readily understood.

Although changes in the cell proportions in the direction of increased numbers of ripe acidophils and basophils are observed in a large variety of clinical conditions, a marked loss of granules is seen only when there is a definite alteration in the hormonal balance. A disturbance of the androgen-estrogen ratio can account for the degranulation of the chromophile cells in pregnancy, in disturbances of gonadal function, and in the hormone-injected animal. The changes in the basophil cells in Cushing's syndrome (5) are probably secondary to a more complex disturbance in the metabolism of the steroid hormones.

It is of interest to note that in the 3 cases receiving the benzoate ester there was a marked hyperplasia of the anterior pituitary, whereas only one of the estrone-injected cases revealed extensive changes. However, the number of cases is too small to justify conclusions regarding the relative potency of the two estrogens. In addition to the rate of absorption and duration of action of the two preparations, one must consider the production by the organism of androgens or other steroids to counterbalance the excess of estrogen. Also, the rate of inactivation of the estrogen by the liver must play an important rôle. Impaired liver function would thus enhance the effect of any given dose of estrogen. There probably are other factors which influence the individual response.

This series of cases is too small to evaluate the time factor in relation to the degree of cellular reaction. It is of interest to note that *case 13*, the pituitary of which showed the most pronounced acidophil changes, received only 11.6 mg. of estradiol benzoate in 9 days, whereas the pituitary of *case 9*, which was treated with 43.8 mg. of the same estrogen over a period of 42 weeks, revealed a less marked change in the acidophils. The influence of age, sex and underlying disease also cannot be judged because of insufficient data.

The 4 cases that were classified as marked hyperplasia showed individual features that deserve special comment. *Case 3* showed the most

pronounced changes in the basophil cells, not only in this group of cases, but with one exception (13) in the several hundreds of pituitary glands that I have examined. The basophil cells were increased to about 30 per cent (normal 5-10 per cent), but only half of them contained ripe granules. The degranulated basophils were large and polygonal, with large vesicular nuclei and a watery, finely granular faintly basophilic cytoplasm (fig. 1). Castrated cells with small dark nuclei also were numerous. The acidophils in this case also exhibited marked pleomorphism and granule loss. The changes are remarkable and 34 days had elapsed after the last dose of estrogen. Slight amyloidosis of the liver was present in this individual, and this may have interfered with the inactivation of the estrogen, resulting in an intensification of its effect. There were no apparent clinical or morphologic changes in the other endocrine organs that might have accounted for these alterations in the anterior pituitary.

*Case 13* revealed the most extensive loss of acidophil granules. The remaining granular acidophils stood out prominently as small islands among sheets of transition cells (fig. 2). Some of these degranulating acidophils had a very bizarre morphology, and under high magnification appeared almost neoplastic. This patient had received in a period of 9 days 11.6 mg. of estradiol benzoate. Although a complete autopsy was not performed, it seems reasonably certain that these cytologic changes were related to the administered estrogen, since I have never seen as marked acidophil degranulation in any other pituitary.

*Case 8* is of interest because of the alterations in the basophil cells. Granule dispersion was prominent and cells approaching the colloidal type were fairly numerous. One basophil cell was observed in the prophase stage of mitotic division. Although mitosis is not rare in the anterior pituitaries of animals receiving estrogens, or after thyroidectomy, I have never before observed it in a human gland.

Finally, *case 9* deserves attention because of the prolonged administration (10 months) of estradiol benzoate to a man. There were no morphologic changes in the other organs. The anterior pituitary revealed fairly extensive granule loss and a minute, localized nodule

watery, degranulated acidophils at the anterior pole.

Investigation of a much larger series of patients under a greater variety of experimental conditions would be necessary to determine the minimal dose of estrogen necessary to produce morphologic changes in the human anterior pituitary. Relatively huge doses of estrogen over a relatively long period of time are necessary to produce structural changes in the animal pituitary. On the basis of available data, it is likely that the amounts of estrogen employed in the present studies were sufficient to produce changes in the hormonal balance. Corner (14) estimated, on the basis of comparison with the *Macacus rhesus* monkey that the human adult female secretes about 3000 I.U. (300 gamma) of estrone daily. Even if this estimate should be too low, the androgen-estrogen ratio must have been altered in all 4 female patients by the dosage of estrogen used. It is obvious that the change in the hormonal balance must have been even greater in the case of the males in whom the secretion of estrogen is normally at a very low level.

The problem arises of whether the structural alterations produced in the anterior pituitary by estrogens represent a stimulation or a depression of function. Zondek (3) stated that estrone could either activate or depress the function of the anterior lobe, depending upon the amount of hormone administered and the duration of its action. Small doses stimulated, while large doses depressed function. If the administration of estrogen in animals was prolonged, the gonadotropic function of the pituitary was first depressed, and later the elaboration of the growth factor was decreased. However, large amounts of hormone were necessary to inhibit the growth of young rats. For example, 2900 I.U. of estrone or estradiol benzoate in oil given subcutaneously over a period of 4 months to rats weighing 25 gm. had no effect on body growth. An equivalent dosage in a young child would be about 3,000,000 I.U. of the hormone over a proportionately longer period. However, 12,000 I.U. of aqueous estrone within 5.5 weeks was accompanied by a reduction of 9.6 per cent of body weight. This would be approximately equivalent to 12,000,000 I.U. of estrone to a young child.

It is of interest to note (3) that the hypophyses of eunuchoid dwarf rats contained no less gonadotropic factor than those of control animals. Zondek thus concluded that there had been interference only with the delivery into the blood stream of the gonadotropic factor. However, Severinghaus (1) stated that there was a decrease in the sex stimulating potency of pituitary glands showing basophilic degranulation after pregnancy urine extract injections. It is difficult to reconcile these two views. One cannot rely upon implantation experiments to determine the functional status of the anterior pituitary, for only hormone storage is thus measured. Assay of a hyperactive or an exhausted gland would both show a low hormone content, while a resting gland would contain a high hormone level. There are no accurate methods of assay for the several hormones of the anterior pituitary, all of the biologic tests for tropic factors being only rough approximations. Furthermore, considerable alteration of function can occur without specific morphologic change and *vice versa*. A similar situation obtains in the case of the thyroid gland. The hyperplasia of endemic goiter and that of Graves' disease may be indistinguishable. Hence, one must be very cautious in attempting to estimate the functional status of the anterior pituitary by even the most refined cytologic methods.

In certain cases, however, one may be able to judge anterior pituitary function by combined clinical and anatomic studies. For example, it is accepted that acromegaly is caused by a hyperfunction of the acidophil cells. One may then reason that the hyperplasia and degranulation of the acidophils which occurs in the anterior pituitary during pregnancy represents hypersecretion, since acromegaloid features are not uncommon during the gravid state.

Clinical experimentation may offer some clue as to the amount of estrogen necessary to depress the gonadotropic function of the anterior pituitary. According to Zondek (3), 70,000 to 600,000 I.U. of estradiol benzoate can bring about inhibition of menstruation for from 7-70 days. There is a considerable degree of individual variation in the dosage of estrogen necessary to produce this effect.

At this point, it be pertinent to

Zondek's case of massive estrogen administration to a young woman (4). This was an instance of post-operative metastatic mammary carcinoma in a 26-year-old woman. She received 0.6 gm. (6,000,000 I.U.) of estradiol benzoate over a period of 60 days. The estrogen was given on the 14th day of the cycle and the expected menses was delayed 25 days and was scanty (one day). The next bleeding occurred 32 days later, and lasted only several hours. Death occurred on that day. At autopsy, the pituitary gland weighed 710 mg. and showed a large, circumscribed area of acidophil hyperplasia in the upper posterior zone and occupying half of the entire anterior lobe. The endometrium showed glandular cystic hyperplasia, hyperemia and hemorrhage. The cervix revealed a papillary erosion. The ovaries had no primary or ripening follicles and no corpus luteum. The other organs showed no changes. Zondek concluded that the ovarian changes were due to depression of the gonadotropic function by the estrogen. The changes in the cervix and endometrium were local effects due to the huge doses of estrogen. According to Zondek, it is thus possible to induce functional castration by large doses of estrogenic hormone.

#### SUMMARY

Nine male and 4 female patients were treated with estrogenic hormone over varying periods of time and the pituitary glands were examined cytologically. All 3 of the cases receiving the estradiol benzoate and one receiving estrone showed marked hyperplasia of the chromophil cells. The cytologic structure resembled that produced in animals by estrogen injection. No changes were observed in the other organs examined.

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## DOES ANDROGEN THERAPY ENDANGER THE TESTIS?

ACCORDING to existing evidence, administration of androgens can either depress or enhance spermatogenesis. What conditions determine the results are not yet well understood.

Important evidence indicating testis damage by androgens has been presented by Moore and Price.<sup>1</sup> They showed that when 0.1 mg. of testosterone propionate was administered daily to young rats for a period of 3 weeks, the resultant testis weights were 20 to 25 per cent of those of the littermate controls and that the germinal epithelium was markedly injured. In the immature rats in Moore's experiments the smallest dose of androgens produced the greatest testis damage while the largest doses produced the least damage. In the adult rat, testicular hormone has never been shown to damage the testes. A warning that deleterious effects to the testes might follow the use of androgens in man seemed timely, especially when various workers<sup>2,3</sup> observed clinically that injections of testosterone propionate in doses approximating 75 mg. per week over a period of two or three months depressed the sperm count, and at times to very low levels. However when semen examinations were repeated following cessation of therapy, the sperm counts rose again to their original height or exceeded it. Similar results were seen following the oral administration of methyl testosterone. The effects of small doses of androgens in man is still indeterminate.

Walsh<sup>4</sup> in 1934 showed that when large amounts of androgens were given to hypophysectomized rats not only did the usual rapid testicu-

lar degeneration fail to occur but also spermatogenesis was maintained. Nelson<sup>5</sup> corroborated and extended these findings. Later he showed that testicular regeneration could be evoked by injections of androgens plus adrenal cortical hormone even weeks after hypophysectomy without treatment. Other experimental data showing that androgens support spermatogenesis include the findings that hypophysectomized ground squirrels show testicular activity after treatment with androsterone and testosterone.<sup>6</sup> If the ground squirrel in a sexually immature state is treated with androsterone or testis extracts, sperm will be produced earlier than normal.<sup>7</sup>

Cuyler<sup>8</sup> observed that in certain birds which appeared to be capons the comb growth behaved in an unusual way following injections of androgenic urinary extracts. After showing marked growth the comb regressed very little or none at all between injections, so that with each successive injections the comb more closely simulated that of a normal cock until a fully normal appearance was attained. Such birds at autopsy always showed testis tissue and frequently had an hypertrophied mass of tissue much larger than the original testis. Such apparent testis stimulation may not be specific, however, since testicular degeneration consequent to hypophysectomy may be prevented by progesterone<sup>9</sup> and by yeast.<sup>10</sup> It is interesting in this respect to note that in rams sperm production may be stimulated by stilbestrol also.<sup>11</sup>

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<sup>6</sup> WELLS, L. F., AND L. T. GOMEZ. Hypophysectomy and its effects on male reproductive organs in wild mammal with animal rut (*Citellus*). *Anat Rec* 69: 213 1937

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<sup>8</sup> CUYLER, W. K. Personal communication

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<sup>2</sup> HECKEL, N. J. Production of oligospermia in man by use of testosterone propionate. *Proc Soc Exper Biol & Med* 40: 658 1939

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<sup>4</sup> WALSH, E. L., W. K. CUYLER AND D. R. McCULLAGH. Physiologic maintenance of male sex glands, effect of andro-  
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In rats, very low and very high doses of androgens may stimulate spermatogenesis while intermediate doses have depressing effects. Rubinstein<sup>12</sup> showed that when immature rats were given doses of testosterone propionate of 5.0 micrograms daily, the testis weights increased, whereas doses of 50.0 micrograms caused a decrease. Using higher doses, Shay<sup>13</sup> found that 3.0 mg. per week inhibited sperm maturation in rats, while 30.0 mg. per week was followed by increased weight of the testes and stimulation of sperm production.

In man the chief indication for the use of androgens is not in the treatment of sterility. The bulk of evidence indicates a depressing effect of the materials upon spermatogenesis. Clinical evidence that small doses of androgen

may be useful in human sterility is too meagre to warrant the general use of these agents for this purpose. For the present, then, the most practical clinical use of androgens is as replacement therapy where clear evidence of androgen deficiency exists.

In boys in whom adolescent changes are delayed, gonadotropins are usually indicated. If these substances fail to stimulate the testes to the production of normal quantities of androgens, then the administration of androgens themselves may be warranted. Inhibition of sperm production should be considered as a possible result of such treatment. In men repeated sperm counts serve as an index of fertility. In boys, however, such a test is not obtainable. In order to maintain any potential fertility and to avoid reducing chances for fertility in the future, courses of treatment should be interrupted by periods of rest.

Clinicians should remember that the problem is still in the stage of clinical experimentation.

E.P.McC.

<sup>12</sup> RUBINSTEIN, H. S., AND A. A. KURLAND: Effect of testosterone propionate on rat testis. *Endocrinology* 28: 495. 1941.

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# LETTERS TO THE EDITOR

## NUTRITIONAL DEFICIENCY AND MATERNAL BEHAVIOR

TO THE EDITOR

In a letter to the Editor in the March issue of this journal, Dr David M Levy commented on studies he has made on mothers of children under treatment for behavior problems. He found that there is a relationship 'between the habitual number of days of menstrual flow and the strength of the maternal feeling' and that 'a significantly higher proportion of strong maternal impulses appeared in the woman having a flow of 6 to 8 days than in the group flowing from 2 to 4 days.'

Observations previously made in animals, that the liver loses its ability to inactivate estrogen in vitamin B complex deficiency,<sup>1,2</sup> led us to investigate the relation of nutritional deficiency to the occurrence of clinical syndromes associated with an excess of estrogen. In a study already reported,<sup>4</sup> and in others now in progress we have observed that women with pro-

longed menstrual periods usually suffer also from premenstrual tension and that deficiency of the vitamin B complex is concerned in the etiology of both syndromes. The excessive irritability in these women often persists through the entire month, becoming more severe as the estrogen level rises further in the latter part of the intermenstruum. This would seem to be an important factor in inducing behavior problems in the children. Several patients whose chief complaint was menorrhagia, spontaneously expressed concern because they had been becoming increasingly short tempered with their children. This was accompanied by an attitude of obvious over solicitude.

Treatment of the nutritional deficiency in these patients with vitamin B complex in adequate dosage orally, or orally and parenterally, led not only to diminution in the amount and duration of the menstrual flow but also to prompt disappearance of the excessive irritability.

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<sup>1</sup> BISKIND, M S, AND G R BISKIND. *Science* 94: 462

1941  
<sup>2</sup> BISKIND, M S, AND M C SHELESNYAK. *Endocrinology* 30: 819 1942

<sup>3</sup> BISKIND, M S, AND G R BISKIND. *Endocrinology* 31: 109 1942

<sup>4</sup> BISKIND, M S. *J Clin Endocrinology* In press



# Abstracts of

## CURRENT ENDOCRINE LITERATURE

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### BOOK REVIEW

LEMONS TORRES, ULISSES.

Hyperthyroidism and its treatment. São Paulo, 1942, 342 pp.

The author distinguishes six different types or grades of hyperthyroidism: (1) hyperthyroidal constitution; (2) Graves' disease, with 5 subgroups; (3) hyperthyroidism caused by general hormonal disequilibrium, especially of pituitary origin; (4) by adenoma; (5) by inflammation; (6) by neoplasm. Various types are illustrated by case reports (15 in all) which excel in their completeness of personal histories and clinical and laboratory data and which are supplemented by photomicrographs showing the structure of the removed thyroid. Many of the proposed theories, e.g., iodine-Basedow as a consequence of iodine treatment of a non-toxic adenoma, are culled from debatable literature. In his introductory chapters on the anatomy and physiology of the thyroid and also in most of the rest of the accompanying text, the author tries to account for as much of the abundant literature as his limited space permits. The reader is impressed with the variegated and often contradictory theories advanced on the normal and pathological physiology of the thyroid.—A.E.M.

### ADRENALS

HASELTINE, S. L.

Later report on suprarenal gland in the treatment of glaucoma, progressive myopia, and some allergic conditions. *J. Am. Inst. Homeotherapy* 36: 85. 1943.

Oral administration of 8 to 15 mg. of adrenal gland, 1 to 3 times a day, is of value in these conditions and in hay fever, asthma, vernal catarrh and eczema. Eight case reports are presented.—*Courtesy Biol. Absts.*

HENI, F.

The sublingual administration of desoxycorticosterone in the treatment of Addison's disease. *Deutsche med. Wchnschr.* 68: 162. 1942

Three cases of successful use of the acetate DCA, by sublingual administration in Addison disease are reported. Absorption is sufficient but the dose must be about  $\frac{1}{3}$  higher than in intramuscular administration. Overdosage may result from continued administration of 10 mg. or more. Blood studies are included.—*Courtesy Biol. Absts.*

HENI, F.

Problems in the utilization of desoxycorticosterone and similar substances in actual cortical insufficiency. *Deutsche med. Wchnschr.* 68: 318. 1942.

Desoxycorticosterone acetate affects salt and water metabolism more strongly than the carbohydrate metabolism, in Addison's disease. The effect on K metabolism is less than that on Na and it is suggested that carbohydrate metabolism is influenced by potassium concentration. DCA did not completely restore health in 4 patients with severe Addison's disease, although it is highly effective in mild or moderate cases. Progesterone has a beneficial effect on carbohydrate metabolism in severe Addison's disease; testosterone and estrone increase general tone only in mild cases. These related sterones do not act on salt metabolism but increase the glycogen reserve of muscle. Progesterone may be used in certain severe cases of Addison's disease in which DCA produces disturbances of water and salt metabolism. The effect of the various agents on glucose tolerance is compared.—*Courtesy Biol. Absts.*

KOSTER, H. AND L. P. KASMAN.

Effect of desoxycorticosterone acetate in post-operative shock. *Arch. Surg.* 45: 272. 1942.

200 patients operated on for conditions such that shock might reasonably be expected to develop during or after the operation were studied. 100 alternately chosen patients were treated with desoxycorticosterone acetate, one to two days preoperative and ten to twelve days postoperative. The other 100 patients were given parenteral NaCl solution. Mortality rate in the treated and control groups was used as the criterion of effectiveness of therapy. There was no evidence that desoxycorticosterone therapy prevented or influenced the shock state favorably.—*D.A.M.*

SARASON, E. L.

Morphologic changes in the rat's adrenal under various experimental conditions. *Arch. Path.* 35: 373. 1943.

Changes in weight of adrenals relative to body weight and lipid deposition, observed histologically, were studied in rats subjected to (1) desoxycorticosterone acetate, (2) hypophysectomy, (3) castration, (4) inanition, (5) high protein and (6) high potassium diets and (7) stilbestrol. Administration of 2 mg. of desoxycorticosterone acetate per day for one month resulted in atrophy of the adrenal in the male but not in the female. In both, the zona glomerulosa was shrunken and depleted of lipid. In the atrophy following hypophysectomy the zona fasciculata was shrunken and the zona glomerulosa became slightly hyperplastic. Administration of desoxycorticosterone acetate to these rats resulted in further atrophy of the adrenal associated with shrinkage and depletion of lipid of the zona glomerulosa. This indicates that adrenal atrophy following desoxycorticosterone acetate is not mediated through the pituitary. Acute inanition in the female resulted in moderate adrenal hypertrophy accompanied, in about half the animals, by depletion of cortical lipids. Adrenals of rats fed for a month on a diet containing 45-50% protein and of rats receiving, after a 24 hour fast, an injection of 5 mg. of stilbestrol per 100 g of body weight, showed adrenal hypertrophy and some degree of lipid depletion.—*M.L.M.*

SCUDDER, J. AND R. H. E. ELLIOTT.

Controlled fluid therapy in burns. *J. South. M. and Surg.* 104: 651. 1942.

Case report illustrating severe hemoconcentration, electrolyte changes, acidosis, hypoproteinemia, sodium loss and hyperpotassemia which

occur early in the burn syndrome; and the hyperbilirubinemia, hypocholesteremia and anemia seen later. Therapy included serum, salt, adrenal cortical extract, glucose, oxygen, plasma, blood transfusions, and a high protein and high vitamin diet. The successful use of cortical extract is emphasized.—*D.A.M.*

TAYLOR, C. E., AND B. H. KEAN.

Waterhouse-Friderichsen syndrome on Isthmus of Panama. *Am. J. Dis. Child.* 65: 426. 1943.

Two cases in mestizo infants are reported. The first, a girl aged 25 days, is the youngest except one in the literature. At postmortem she showed extensive bilateral adrenal hemorrhages, a congenital polycystic kidney (left), moderate congestion of the lungs, moderate congestion of the leptomeninges, severe congestion of the mucosa of the larynx and trachea, small bilateral subconjunctival hemorrhages, small cysts of the base of the tongue, cyanotic mottling of the skin, a relatively large normal thymus, and a total absence of lesions in the periadrenal tissue. The second, a girl of 2 months, was found at autopsy to have hemorrhage of the left adrenal, bilateral suppurative otitis media, severe tubular degeneration of the kidneys, malnutrition, hypoplasia of the thymus, and no hemorrhage in the periadrenal tissue. In both cases the hemorrhage had destroyed the medulla and a large part of the cortex of the glands. The meningococcus was not demonstrated in either case. Both patients had an acute clinical course with high fever, gastro-intestinal and respiratory symptoms and collapse. These are the first cases to be reported from Central America and bring the total of published cases to 107.—*E.C.R., Jr.*

## ENDOCRINE GENERAL

BICKERS, W.

Primary dysmenorrhea. *South. M. J.* 36: 192. 1943.

The normal and dysmenorrheic patient have been compared according to general body structure, psychic factors, age, family history, menstrual regularity, endocrine status as shown by the consistent presence of a corpus luteum, endocrine status, anatomy of the uterus, histology of the uterus and myometrial physiology. The only difference found between the two groups was the constant alteration in myometrial physiology in the dysmenorrheic uterus. A condom balloon was inserted into the uterus, and connected through a catheter to a kymograph. Tracings of uterine

contracts during menstruation were taken on 17 dysmenorrheic patients and a group of normal control. Myometrial spasm was demonstrated in the dysmenorrheic group. This spasm could not be abolished by atropine, ephedrine, epinephrine, calcium gluconate, and benzedrine sulfate. A new spasmolytic, non-narcotic, pavarine-like drug, pavatrine, abolished myometrial spasm and inhibited uterine contractions in about one third of the dysmenorrheic uteri. Estrogens, progesterone and testosterone did not alter the pattern of human motility in the human uterus. The author recommends a flexible stem pessary, inserted on the last day of menstruation, which will act as a foreign body to stimulate a congenitally defective myometrium to expulsive contractions, with improvement in the myometrial physiology. In a majority of the patients with dysmenorrhea the uterine spasm will be abolished after the pessary has been in place for 6 weeks.—*H.W.*

BRONSTEIN, I. P., L. J. HALPERN AND A. W. BROWN.

Obesity in children. *J. Pediat.* 21: 485. 1942.

Of a large group of children referred with tentative diagnoses of Fröhlich's syndrome, studies of 46 children, ranging from 4 to 15 years, comprise this report. History and physical and laboratory examinations of each child on admission and at regular intervals thereafter, over an observation period ranging from 6 months to 6 years, were conducted to establish any evidence of glandular dysfunction as a possible basis for obesity. None was found.—*Courtesy, Child Development Abstracts.*

BRONSTEIN, I. P., A. LUHAN AND WM. B. MAVRELIS.

Sexual precocity associated with hyperplastic abnormality of the tuber cinereum. *Am. J. Dis. Child.* 64: 211. 1942.

Report of a case of a 22-months-old girl exhibiting precocious sexual development, "in whom necropsy revealed what was interpreted as an ectopia of brain tissue between the infundibulum and the mamillary bodies."—*Courtesy, Child Development Abstracts.*

CANTILO ENRIQUE AND CARLOS FERNANDEZ SPERONI.

Endocrinopathies, X. Discussion on two amenorrheas. *Semana méd.* 49, II: 489 (1942).

The first case appeared to be of the asthenic hypoadocrine type but on the basis of well developed genitals with pubic hypertrichosis, a

diagnosis of hyperovarian secretion with pituitary inhibition was made. The second patient of pyknic type, showed male distribution of pubic hair and uterine hypoplasia. In this case pituitary overactivity was diagnosed. The first patient had a fasting glucemia of .088 and of .095 after glucose ingestion; the corresponding figures in the second patient were .101 and .285 gm.%. The first patient received 10 mg. progesterone daily, the second 3 injections of estrogen per week (5 mg. each). The treatment was continuous until menstruation occurred. For stabilization of the menstrual cycle, the first patient received treatment with a FSH preparation combined with chorionic gonadotropin during the first part of the cycle. The second patient was treated with estrogen during the predecidual phase. Permanent cure of the amenorrhea was obtained in both cases.—*A.E.M.*

DEMING, C. L. AND J. T. MACLEAN.

The incidence of pyelonephritis in successive pregnancies. *J. Urol.* 49: 236. 1943.

This paper is a statistical and critical study of 68 cases of pyelonephritis associated with pregnancy, representing 74 infections, 65 of which occurred during pregnancy and 9 of which developed post partum. Nearly two-thirds of all the cases occurred in the first and second pregnancies. The incidence of infection increases each month, with the maximum occurrence at the fifth and sixth months of pregnancy, which parallels the incidence of occurrence of dilation of the ureter. Both parallel exactly the increased excretion of estrogen and pregnanediol by the placenta during pregnancy. Only 25 per cent of the cases were "cured" at term, yet within 2 weeks of emptying the uterus, 90 per cent were asymptomatic and free of infection.—*H.W.*

FOLLEY, S. J.

"Ghost" formation in subcutaneously implanted tablets of synthetic oestrogens. *Nature* 150: 403. 1942.

Tablets of diethylstilbestrol and hexoestrol implanted in cattle 3 months have the cortex infiltrated with a substance that is chiefly scleroprotein and form an ether-alcohol insoluble membrane that retards absorption of the estrogen from the implant.—*Courtesy Biol. Absts.*

FOLLEY, S. J.

Retarding effect of ghost formation on absorption from subcutaneously implanted tablets of hexoestrol. *Nature* 150: 735. 1942.

Disk-shaped 1-gm. tablets of hexoestrol implanted subcutaneously in cattle maintained a near absorption curve for the first 10 to 15 days; then the curve continued to fall so long as the experiment lasted. This retardation of absorption is attributed to infiltration of the cortex of the implant by a relatively insoluble protein which forms a "ghost" around the tablet.—*Courtesy Biol. Absts.*

DRBSCH, R.

Treatment of gastric ulcers with progesterone and other cholestenone derivatives. *Deutsche med. Wchenschr.* 68: 417. 1942.

Estrone is known to have a beneficial action on gastric ulcers due to a direct trophic effect on gastrointestinal epithelium and an indirect osmolytic effect on smooth muscle. Progesterone, in daily injections of 20 mg., is not as effective but does not cause mastodynia or loss of potency in males. A mixture of androstenedione and progesterone, in the same daily dose, is also as active but is useful in treating gastritis. Isoxycorticosterone acetate, 10 to 20 mg., had little effect on ulcers but it is believed that higher doses should have a marked effect, at least in gastritis.—*Courtesy Biol. Absts.*

DUAK, E.

The present status of gynecological organotherapy. *South. M. J.*, 36: 145. 1943.

This paper is a long review article, comparing the present status of organotherapy in gynecology with that existing 20 years ago. While our knowledge of reproductive endocrinology has enormously increased during the last 25 years, there has not been a corresponding advance in gynecologic organotherapy. There has been no noteworthy improvement in the treatment of amenorrhea. Organotherapy is frequently of auxiliary value in the treatment of dysmenorrhea and functional bleeding. Progesterone is generally reported to have definite value in the treatment of threatened and habitual abortion. Organotherapy is rational and effective in the treatment of the menopausal vasomotor symptoms, gonorrheal vulvovaginitis of children, and nile vaginitis. The advances made in the knowledge of reproductive endocrinology have facilitated intelligent interpretation of clinical problems and may, each year, add to our therapeutic armamentarium.—*H. W.*

LECHER, J. D. AND H. TUCHEWICZ.  
Premenstrual state in young girls. *Am. J. Dis. Child.* 65: 269. 1943.

The authors studied a 10 year old girl with a persistent vaginal discharge that had been suspected but never proven to be due to gonorrhea. They decided that this discharge was part of the normal premenarchal state, an observation which has been described before only in the German literature (by Soeken). The authors then investigated 49 other girls ranging in age from 8½ to 14 years and concluded that the premenarchal changes: (1) are first noticed between the ages of 8 to 13 years (mean 11 years 4 months); (2) occur usually one month to two years (mean 10 months) before the onset of menses, but may appear suddenly only one week before menarche; (3) are characterized by: a) a white, caseous exudate on the vulva and in the vagina, a swelling and a graying of the hymenal ring, a rugate and pale appearance of the vaginal wall and a normal appearing cervix; b) a change in the reaction of the vaginal secretion from alkaline to acid; and c) a change in the type of flora from cocci to bacillary (although acid-forming enterococci are occasionally found with or without the bacillary group); (4) usually but not always precede other signs of puberty such as development of the breasts and growth of the vulvar hair; (5) persist after menstruation; (6) are similar to the changes induced by estrogen therapy; (7) are probably responsible for the spontaneous cure of gonorrheal infection; and (8) are often mistakenly diagnosed as gonorrheal vaginitis.—*E.C.R., Jr.*

PREISSECKER, E.

Studies on the tolerance of stilbene. *Deutsche med. Wchenschr.* 68: 428. 1942.

Choline increases tolerance of women to diethylstilbestrol and its dipropionate. Side effects are less frequent with a double compound of diethylstilbestrol and choline than with diethylstilbestrol alone. Studies with other esters of stilbestrol are reviewed.—*Courtesy Biol. Absts.*

SCHITTENHELM, A.

A critique of hormone therapy. *Deutsche med. Wchenschr.* 68: 33. 1942.

Modern applications are reviewed for pituitary, thyroid, adrenal cortex and sex hormones, as well as for insulin and diethylstilbestrol. In the introduction, a warning is given of the inapplicability to diagnosis of the interferometric method of the Abderhalden reaction.—*Courtesy Biol. Absts.*

SCHNEEBERG, N. G., W. B. LIKOFF, AND I. E. RUBIN.

The pituitrin concentration test of renal function. *J. Lab. & Clin. Med.*, 28: 757. 1943.

In a series of 100 unselected hospital cases, 4 procedures for testing renal function were compared: the Fishberg test; the Volhard dilution test; the Volhard dilution test plus 0.5 cc. surgical pituitrin; and the pituitrin concentration test of Sodeman and Englehardt. All procedures were performed in 25 patients, and the Fishberg and pituitrin concentration tests in the remaining 75. There was a 90 per cent correlation in the results obtained by the Fishberg technic and the pituitrin concentration test. In 4 cases the pituitrin test failed entirely, and in 6 it apparently reflected the condition of the kidney more accurately than did the Fishberg procedure. When the specific gravities of the urines ranged between 1.015 and 1.025, statistical analysis of the results showed the possibility of considerable disagreement between the 2 tests. The authors believe many more cases must be studied before the relatively simple pituitrin test can be used in place of the Volhard or Fishberg procedures in the true evaluation of kidney function.—*T.H. McG.*

SEXTON, D. L.

Emaciation and endocrine dysfunction. *South M. J.* 36: 276. 1943.

Eight cases are presented of patients whose chief findings were emaciation, weakness, and anterior pituitary failure, the thyroid, adrenals and gonads being markedly affected. In 6 of the 8 patients, history of a definite psychological disturbance was elicited, while in the other 2 the onset was insidious. From the experimental and clinical evidence available, functional pituitary failure may follow inanition. The clinical signs are not unlike those seen in early Simmond's disease, with anatomical destruction of the anterior hypophysis. The author believes there is an inherent weakness in the pituitary gland that is functionally depressed by inanition, producing gastric disturbances and anorexia as does Simmond's disease. He recommends correction of the psychic upset, and support of adrenal deficiency, with substitutional hormone therapy added as needed.—*H.W.*

SHUTE, EVAN

Influence of estrogens on genuine pre-eclampsia and eclampsia. *Am. J. Surg.* 59: 478. 1943.

Presented in detail are case reports of the convulsive eclamptics and of eight true pre-eclampsia. One of the latter was induced and remained ambulatory. All cases were favorably influenced by administration of estrogens, including estradiol benzoate and diethylstilbestrol. This therapy is more effective in the prophylaxis than in the control of convulsive eclampsia could be anticipated. Author believes that blood estrogen assays are essential to recognition of true pre-eclamptic state since administration of estrogens to unproven pre-eclampsia does no good and may do some harm.—*D.A.M.*

SHUTE, EVAN

Vitamin E in the prophylaxis of abruptio placentae. *Surg., Gynec. and Obstet.* 75: 515. 1942.

Case reports are presented to show that abruptio placentae can be foreseen during pregnancy by means of a blood estrogen assay, the signs disappear promptly if vitamin E is administered at once; "the vitamin E used must be a potent preparation. The dose usually rises as pregnancy proceeds and must always be the dose required to control symptoms if any particular woman's pregnancy. . . . It must be given until delivery."—*Author's Abstract.*

SHUTE, EVAN.

Vitamin E in habitual abortion and habitual miscarriage. *J. Obst. and Gynec. Brit. Emp.* 49: 534. 1942.

Brief details are presented of all the pregnancies, both before and during treatment with vitamin E or other agents, of 17 women with histories of true habitual abortion and 5 with habitual miscarriage. No evidence was found that vitamin E, even when given in large doses, was of any value in the treatment of habitual abortion. There was some evidence that vitamin E therapy might be of some value in the treatment of habitual miscarriage.—*Author's Abstract.*

TALBOT, N. B., A. M. BUTLER, R. A. BERNARD, P. M. RODRIGUEZ AND E. A. MACLACHLAN.  
Excretion of 17-ketosteroids by normal and abnormal children. *Am. J. Dis. Child.* 65: 36. 1943.

A series of measurements of the urinary excretion of 17-ketosteroids has been made on normal subjects ranging in age from a few hours to over 47 years. Of these, 31 were made on 31 girls ranging in age from 4 to 18 years; 69 were made on 69 boys ranging in age from a few hours to 1

ars The output is low from birth to approximately 10 years, and then gradually rises as the boys approach 18 years. Boys did not excrete significantly greater amounts of these substances than girls suggesting that the adrenal cortex is the chief site of origin of the 17-ketosteroids during childhood. The rise in the output after 10 years implies a relation between the secretory activity of the adrenal cortex and growth and development. From the normal range it is possible to tell whether a given value is abnormally high at any age, but since values approximating 0 may be considered normal for children under 10 years, detection of abnormally low excretion under that age is not possible. Children of 12 years should excrete at least 1 mg of 17-ketosteroids daily, of 18 years approximately 9 mg daily. Day to day variation in the excretion by a single subject was investigated. An analysis of assays on 2 normally menstruating (adult) women showed that two thirds of the values fell within  $\pm 15$  and  $\pm 12$  per cent of the average value for each subject, respectively. In no instance did any value obtained for one subject deviate from her average value by more than  $\pm 30$  per cent. Approximately similar results were obtained in the assays of a normal man and of two children. A tendency toward a moderate elevation in output of 17 ketosteroids was observed in apparently "normal" children with physiologic sexual precocity and in 7 abnormally overweight children. These latter also were found to have accelerated development and growth, suggesting that excessive obesity may favor a hyperexcretion of 17 ketosteroids. Abnormally low excretion is found in children over 12 years whose growth and development were retarded, including 9 patients with presumable deficiency of the anterior lobe of the pituitary gland and 12 patients with hypothyroidism who were receiving thyroid therapy. This suggests either that more thyroid medication is required for the excretion of a normal amount of 17-ketosteroids than for "adequate" clinical response, or that "hypothyroidism" is not necessarily a simple disease, which is characterized only by a lack of thyroid hormone. The excretion of 17 ketosteroids by 13 patients with mongolism was not consistently normal. In adults, 89 determinations were made on 4 normal women, and 12 on 3 normal men. The women had values which corresponded closely to those obtained for children 17 to 18 years old (average 7 mg). Men excreted more (average 11 mg) than women or older children. *E C R, Jr*

VAN WAGENEN, G, AND R H JENKINS

Pyelo ureteral dilatation in successive pregnancies *J Urol* 49 228 1943

The demonstrable dilatation of the ureter which occurs in approximately 80 per cent of all pregnant women has been termed "physiological hydroureter of pregnancy." Stasis caused by this facilitates bacterial invasion and eventual pyelitis. The writers have previously shown that ureteral dilatation also occurs in the later months of pregnancy in the rhesus monkey, and persists after surgical removal of the fetus, in one case making its appearance three months after the fetus had been removed. In the present paper the urinary tracts of 10 monkeys (*macaca mulatta*) have been visualized by excretory urography through 37 normal pregnancies. Dilatation is at a maximum in the first pregnancy, and decreases with succeeding pregnancies. If such conditions exist in the human, infection should be less frequent after the first pregnancy. The hypothesis of a placental endocrine cause of this dilatation was tested by the use of stilbestrol, theelin and progesterone. It was impossible, with the estrogens, in the amount used, to reduce existing dilatation in late pregnancy or to speed up postparturitional regression, nor was premature dilatation induced with progesterone.—H W

WATSON, B A, N YOLTON, AND L RAULS

Sex hormone assays in the menopause their clinical significance *J Lab & Clin Med*, 28 732 1943

Data and conclusions were drawn from the analysis of from 2 to 4 complete 24 hour specimens of urine from each of 28 women with well known signs and symptoms of the climacterium. Of these women, 12 had had an artificial menopause. Estrogens were calculated by the ovarietomized mouse method and reported in gammas of estrone, 17 ketosteroids were estimated by a modification of the Zimmerman method and reported as milligrams of androsterone. The average mean estrone for all cases was about 6.8, for the menopausal group with "flashes," 5.61, and for about those without "flashes," 7.68, the range of values was very wide (1.1 to 22.9). Mean androsterone values were not significantly altered, although individual variations were marked. The cases could be grouped into 3 categories as a result of the hormone determinations. Those with (a) a lack of female sex hormone, (b) a deficiency of male sex hormone, and (c) a sex hormone imbalance with individual values in normal limits,



e.g., low normal male and high normal female, or vice versa. In each instance, therapy was directed with reportedly good results toward replacement of the hormone found to be diminished in the urine. The authors conclude that a satisfactory correlation can be made between the titer of sex hormones of the urine and the clinical results to be expected in treating women with climacteric symptoms.—*T.H.McG.*

WETZEL, N. C.

Assessing the physical condition of children.

III. The components of physical status and physical progress and their evaluation. *J. Ped.* 22: 329. 1943.

The author employs a series of photographs of the same group of children to illustrate the basic meanings that can be attached to physique, development, nutritional grade, and age, separately, and to show how these may be reassembled by means of a "grid" (which he has devised) for the assessment of the physical condition of these children. He emphasizes the ease with which a group can be "screened" by this technique to isolate the individuals who need extensive investigation because of their unfavorable physical state.—*E.C.R., Jr.*

## GONADS

BERGMAN, R. T.

Carcinoma of the prostate: Recent advances in its treatment. *California & West. Med.* 58: 71. 1943.

Hormonal treatment relieved pain in nearly 90% of the author's cases; caused an improvement in appetite, gain in weight, and an actual regression in size of the gland after several months' treatment.—*Author's Abstract.*

BROWN, E.

Treatment of gonorrheal vulvovaginitis with estrogens. *Am. J. Dis. Child.* 64: 211. 1942.

Thirteen cases of gonococcal and 6 of non-specific vaginitis in prepubertal girls treated successfully with estrogens are reported.—*Author's Abstract.*

GOLD, S.

Estrogen therapy in testicular hypofunction. *Canad. M. A. J.* 48: 231. 1943.

Two male patients with diminished sexual potency were treated with estrogenic hormone following a course of testosterone propionate. A third patient received alternate injections of

androgenic and estrogenic hormones. The estrogenic hormones were thought to increase libido and potency; there was no antagonism between the male and female hormones used, in the given quantities and proportions. There was no beneficial effect on spermatogenesis in the patient with total aspermia. The efficacy of the drug was not maintained over a period of time.—*P.H.S.*

JONES, G., E. SEEGAR, G. O. GEY, AND M. J. GEY.

Hormone production by placental cells maintained in continuous culture. *Bull. Johns Hopkins Hosp.* 62: 26. 1943.

Pure strains of cells from human placental tissue were maintained in continuous culture and assayed for cyonin (chorionic gonadotropin) and estrogen made on the supernatant cell free culture medium. Cyonin was demonstrated as indicated by the presence of corpora lutea in the 21-day old rat ovary; estrogen was not present in increased amount over the control tissue culture medium.—*P.H.S.*

LAPIN, J. H., W. KLEIN, AND A. GOLDMAN.

Cryptorchidism, *J. Ped.* 22: 175. 1943.

The authors treated 200 boys for cryptorchidism in their endocrine clinic during the past nine years but are able to report on only 39 boys who were followed for from two to nine years. Successful descent into the scrotum was obtained in only six instances (15.3 per cent). The following conclusions were reached: Treatment of cryptorchid testes is advisable to relieve the deficiency of androgenic hormone formation, spermatogenic activity and the psychological handicap provided a procedure is adopted to minimize the dangers of pubertas praecox, of osseous retardation and of testicular atrophy. The optimal age for treatment is 14 years. A preliminary test of endocrine therapy is fully justified in any cryptorchid testes not clearly ectopic. Chorionic gonadotropic hormones are only ones free from theoretical objections. The maximal dosage should be given in small frequent amounts over a six-week period without any rest period. If the cryptorchid testes do not descend following this dosage and for this period, operation should be immediate and further hormone can be given after the testes is embedded in the scrotum. Ectopic testes should benefit from a similar pre- and post-operative procedure except where complicated by a substantial inguinal hernia.—*M.B.G.*

RUPEL, E.

Prostatic cancer; an evaluation of treatment by castration. *South. M. J.* 36: 251. 1943.

The results of treatment of 26 patients with prostatic cancer by testicular excision, and 8 by stilbestrol treatment. There were three deaths, 10 patients who regressed after immediate improvement had to be placed on stilbestrol, while 11 but one of the patients obtained immediate relief from pain after castration. Stilbestrol had delayed action. A review of the rationale of this treatment is given.—*H.W.*

HOMPSON, W. O.

Endocrine problems in the male. *Nebraska M. J.* 28: 9. 1943.

Discussing treatment of undescended testes, the author says material of choice is chorionic gonadotropin because in most instances, the testes can respond to stimulation. The only exceptions are those cases in which both testes are within the abdominal cavity. It is preferable that treatment be carried out at an early age. When necessary, operative procedures are made easier by pre-treatment with chorionic gonadotropin.—*A.A.M.*

WARREN, S., AND K. W. OLDFATHER.

Interstitial cell growths of the testicle. *Am. J. Path.* 19: 307. 1943.

Two cases of hyperplasia and 2 cases of tumors of the interstitial cells of the testis are reported here is included a detailed survey of the literature on interstitial cells of the testis covering the following topics: in the normal testis, relationship to hormonal influences and hyperplasia of in relation to spermatogenesis. Criteria for classifying either as local tumor or as hyperplasia are presented. Hyperplasia occurs principally at or above 45 years of age in atrophic testicles and is discovered chiefly at autopsy. Local tumors occur predominantly at or below 45 years of age in testicles larger than normal and are generally discovered during life and removed surgically. If the testicle contains an increased number of interstitial cells, especially if the seminiferous tubules are partially or completely destroyed the patient should be carefully followed for more than ten years for the appearance of metastases as indication of malignancy.—*M.L.M.*

VELLS, H. GIDEON.

Seminoma developing in an undeveloped genital anlage. *Arch. Path.* 35: 590. 1943.

A case is reported of complete failure of the

right genital anlage to develop, associated with immaturity of the left genital anlage. At the age of 47 the patient died with a retroperitoneal seminoma, apparently arising in the rest of undeveloped right genital anlage.—*Author's summary.*

ZONDEK, B.

The importance of increased production and excretion of gonadotropic hormone for diagnosis of hydatidiform mole. *J. Obst. & Gynaec. Brit. Emp.* 49: 397. 1942.

Increased excretion of prolactin (FSH), while inadequate for diagnosis of pregnancy in itself, is of value in the diagnosis of hydatidiform mole. A titration value of over 500,000 MU of prolactin A and 200,000 MU of prolactin B (LH) per liter urine is strongly indicative of mole. Urine analyses should be supplemented by serum assay. In positive cases the latter contains quantities of both A and B, higher than that found in urine. Spinal fluid, moreover, which normally is negative for B, becomes positive in hydatidiform mole and in general the higher the titer the more certain the diagnosis. Demonstration of the prolactins in tissues is also of diagnostic importance; a placental tissue titer of over 800 MU per gm. makes diagnosis of malignant degeneration probable, and such diagnosis is certain when values rise to more than 200,000 MU, particularly if the value of A is so elevated. Following pregnancy, persistence of prolactin excretion more than one week post partum is indicative of mole or of luteal cyst. Three cases are presented illustrative of the above generalizations.—*H.O.H.*

## HYPOPHYSIS

ANDERSON, A. AND WM. R. MURLIN.

Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus. *J. Pediatr.* 21: 326. 1942.

The physiologic antagonistic action of adrenal cortical extract and pitressin on the excretion of sodium, chloride, and water has been confirmed in the human subject with diabetes insipidus. Adrenal cortical extract is unable to produce an increased excretion of potassium unless pitressin is supplied. The suggestion is offered that facultative reabsorption of water as induced by pitressin must be in progress before the kidney tubule can selectively excrete sodium and potassium ions.—*Author's Abstract.*

GREENE, B. A.

Posterior pituitary extract in anesthesiology. *Ann. Surg.* 116: 898. 1942.

Author advocates more frequent use of posterior pituitary extracts in operating rooms than has been customary in the past. By their judicious use, the surgeon can secure a more stable peripheral circulatory system, a more relaxed abdominal field, better hydration, less blood loss, more expeditious and less traumatic surgery and a decreased likelihood of postoperative intestinal atony.—*D.A.M.*

LURIE, L. A. AND S. LEVY.

Lawrence-Moon-Biedl syndrome. A report of two cases with unusual combinations of heredofamilial deviations. *J. Ped.* 21: 793. 1942.

Both patients presented a combination of obesity, genital dystrophy, dwarfism, mental retardation, syndactylism, familial occurrence and nerve deafness. One patient in addition presented the symptom of tapitoretinal degeneration. Electroencephelogram showed abnormalities consistent with a rather severe cerebral dysrhythmia. Electrocardiographic tracings revealed normal findings, thus excluding the possibility of congenital heart disease. No skull deformities or skeletal defects were found on roentgenograms. The chemical constituents of the blood were within normal limits.—*M.B.G.*

SHEEHAN, H. L., AND M. G. B. McLETCHE.

Simmond's disease due to postpartum necrosis of the anterior pituitary. *J. Obst. & Gynaec. Brit. Emp.* 50: 27. 1943.

The literature is reviewed and a case is reported of Simmond's disease which arose from postpartum necrosis of the anterior pituitary. It followed a typical clinical course, and the patient remained well nourished. Death occurred 6 years after delivery. Autopsy findings are included. Such cases, as verified by autopsy, now number 48.—*H.O.H.*

WAGNER, R.

Galactose tolerance test in endocrine disorders in children. *Am. J. Dis. Child.* 65: 207. 1943.

The author applied the galactose tolerance test of Althausen, Lockhart, and Soley to 49 children suspected of having reduced pituitary function. These subjects were diagnosed under the headings: hypogonadism, obesity (with the three subdivisions exogenic, constitutional and "Frohlich-like"), cryptorchidism (with or with-

out endocrine features), transitory infantilism, amenorrhea and irregularities of menstruation, acne occurring during puberty, alopecia areata, gigantism, pituitary dwarfism and hepatomegaly of unknown cause. A flat curve was anticipated in these patients because they were assumed to have reduced thyroid function due to decreased output of pituitary thyrotropic factor. The basal metabolic rate was below minus 15 in 11 of the cases. Most of the 49 children showed flat dextrose tolerance curves. The results of the galactose tests were analyzed in terms of the surface area bounded by the plotted curve. Abnormally flat galactose tolerance curves were obtained only for patients with hypogonadism and abnormally high curves only for pituitary dwarfs. The author concluded that the galactose tolerance test was of more value for this series of patients than the dextrose tolerance test. He also determined the rise induced by the galactose in the dextrose content of the blood. The dextrose level was hypoglycemic only in subjects with high galactose tolerance curves. No normal standards for the galactose tolerance test in children were determined; the analysis of the data was based on the standards for adults obtained by Althausen and co-workers.—*E.C.R., Jr.*

## PANCREAS

FISCHER, E., S. MACKLER AND H. MARKS.

Long term growth of diabetic children. *Am. J. Dis. Child.* 64: 413. 1942.

The growth characteristics of a group of 44 diabetic children from low income families, studied over a period of 5 to 10 years or longer, are reported. Of the 42 children whose height at approximately the time of onset of diabetes was known, all but 6 were either average or tall for their age when the disease began. The average rate of growth in height of both boys and girls was below that generally expected in normal children.—*Courtesy, Child Development Abstracts*

JACOB, W.

On the advancement of therapy of diabetes based on clinical and followup results in the last decade. *Deutsche med. Wchnschr.* 68: 410. 1942.

Experience with 1266 diabetics, of whom 57% were ♂, is summarized from 1930 to 1940. Age incidence is noted. Mortality was 6.5% for ♂♂ at an average age of 61 years, and 6.6% for ♀♀ at an average age of 58 years. Fourteen died in coma, and the remainder from various intercurrent diseases or degenerations. Difficulties were

countered in  $\frac{1}{3}$  of the patients in following an insulin regime, and the use of various nostrums noted. Cirrhosis of the liver occurred in 2 patients taking guanidine derivatives. In practice, therapy of diabetes is far from ideal.—*Courtesy of. Absts.*

RSIBAUM, J. D., AND N. SHURE.

Alcoholic cirrhosis of the liver: a clinical and pathologic study of 156 fatal cases selected from 12,267 necropsies. *J. Lab. & Clin. Med.* 28: 721. 1943.

This is a very detailed analysis of 356 cases of alcoholic cirrhosis occurring in 12,267 consecutive topies. The report includes data related to age, racial and sex incidence; alcoholic history; appearance of jaundice and ascites; esophageal varices; variations in blood pressure; the weights of the liver and spleen; pectoral alopecia; the co-presence of carcinoma of the liver; and pancreatic changes. Of endocrine interest are the pancreatic changes. Striking variations in weight of the pancreas were confined to isolated cases, weighing as little as 30 gm., and another as much as 230 gm. In 36.2 per cent, fibrosis of the pancreas was well marked. Five patients had pancreatic calculi. Parenthetically the authors comment that cirrhosis has been found in 50 per cent of all of their autopsied cases of pancreaticohiasis.—*T.H.McG.*

BRIEN, C. S. AND J. H. ALLEN.

Ocular changes in young diabetic patients. *J. A. M. A.* 120: 190. 1942.

Retinopathy was found to occur in 4 per cent of the more than 500 diabetic patients who were subjects of this study. The authors attribute this disorder to the diabetes "since it has the same appearance of that occurring in older patients and it is seen in those in whom no other disease can be found." Diabetic cataract was found in almost 14 per cent of 260 patients under 14 years of age.—*Courtesy, Child Development Abstracts.*

## PARATHYROID

RAKELEY, E.

Late rickets. *Am. J. Dis. Child.* 65: 314. 1943.

A girl is described who at the age of 11 had typical rickets by X-ray. The serum calcium was 12 to 12.5 mg. per cent, the serum phosphorus 2.9 to 3.59 mg. per cent, and the serum phosphatase 29 Bodansky units. Healing was induced after three months by the relatively large dose of 40,000 U.S.P. units of vitamin D. Eighteen

months later x-rays showed decalcification of the shafts of the bones; and during the next year the serum calcium level rose gradually to 15.0 mg., the phosphorus level became low (1.5 to 3.0 mg.), and the serum phosphatase level at first rose to 39 and then fell to 16.8 Bodansky units. These changes were considered to be due to secondary hyperparathyroidism. An exploratory operation was performed, but the parathyroid glands were not identified. The patient then received 800 r of x-radiation to each side of her neck, after which her blood values changed to calcium 12.5 mg., phosphorus 4.2 mg., and phosphatase 12.5 Bodansky units. Six months later the serum calcium was again elevated (15.0) and the serum phosphorus decreased (3.1), while the serum phosphatase had dropped to nearly normal (10.0). X-radiation to both sides of the neck in the same dosage was repeated. Four months later, the calcium was 8.5, the phosphorus 2.23, and the phosphatase 6.7. Clinically the patient was improved; she had grown  $1\frac{3}{4}$  inches, gained 6 lb., and begun menses (age 15). In 18 months since the x-radiation, the serum values have remained normal, the last figures being calcium 10.5, phosphorus 3.7, and phosphatase 6.0. X-rays of the long bones showed recalcification. The author points out that it is impossible to prove whether these alterations were a result of the irradiation or would have occurred without further treatment.—*E.C.R., Jr.*

SPIRA, LEO.

Fluorosis and the parathyroid glands. *J. Hyg.* 42: 500. 1942.

There is a close similarity between the dental changes produced experimentally in the rat by parathyroidectomy and mottled teeth as seen in man and known to be caused by protracted ingestion of toxic amounts of fluorine. In view of the fact that both parathyroidectomy and fluorine produce dystrophies in tissues regulated by the parathyroid glands it is concluded that, in man, mottled teeth, certain dermatoses, mottled nails and alopecia may be due to a disturbance of these glands brought about by the ingestion of toxic amounts of fluorine in drinking water.—*Author's Abstract.*

## THYROID

BARATZ, J. J. AND H. BEHRENDT.

The heart in children with thyroid deficiency. *Am. J. Dis. Child.* 64: 471.

The results of cardiac

genograms and electrocardiographic recordings) of 3 children with thyroid deficiency; and follow-up notes on a patient with myxedema heart, originally examined in 1936, are reported. In none of the 3 more recent patients was the cardiac enlargement as pronounced as in the original patient, but the electrocardiographic changes at the beginning of observation and during treatment were similar in all 4 cases. The pathogenesis of cardiac enlargement associated with cretinism is discussed.—*Author's Abstract*.

CASAUBON, ALFREDO, CARLOS I. GARCÍA DÍAZ AND ANÍBAL LETAMENDI.

Graves' disease in childhood. *Semana méd.* 50: 210. 1943.

Graves' disease in three girls of preadolescent age is described. The treatment consisted in rest, iodine medication and radiotherapy. Cure including regression of the exophthalmos was obtained.—*A.E.M.*

HEREDIA, PABLO.

Angina pectoris of thyroïdal origin. *Semana méd.* 50: 357. 1943.

Among the four possible relationships between angina and thyroid affection only one type is recognized as caused by thyroid disease, namely angina of myxedema with improvement or cure produced by thyroid treatment. Four cases are reported to illustrate this assertion.—*A.E.M.*

HILL, A. M. AND J. E. WEBBER.

Serum phosphatase values in children showing retardation in osseous development and low metabolic rates. *J. Ped.* 22: 325. 1943.

This study confirms Talbot's observation that the serum phosphatase tends to be below normal in children with hypothyroidism. The authors investigated 23 children who exhibited symptoms of mild hypometabolism and who, in addition, showed either marked osseous retardation or low metabolic rates, and found that 20 of them had serum phosphatase values of 5.6 Bodansky units

or less. The normal values in children are: Bodansky—7.5 units (average), 5 to 14 units (range); Talbot—7.2 units (average), 4.5 to 10 units (range); authors—5 to 9.7 units (range based on 14 children). Thyroid therapy causes low serum phosphatase levels to approach the normal range.—*E.C.R., Jr.*

MAY, W.

Treatment of hyperthyroidism with fluorotyrosine. *Deutsche med. Wchnschr.* 68: 164. 1942.

Fluorotyrosine is recommended for hyperthyroidism. Studies are cited on the relation of clinical signs of hyperthyroidism to glycogenolysis; the inhibiting effect of NaF on hepatic glycogenolysis; the partial antagonism between F and I; and treatment of Basedow's disease with fluorotyrosine. Over 3000 hyperthyroid patients have been treated with fluorides. Fluorotyrosine represents a safe agent for treatment of difficult cases as well as for the increasing number of cases of hyperthyroidism due to nervous strain and exhaustion in war. Five case reports are given, in which fluorotyrosine substitutes for iodine in Basedow's disease. The effects of this agent are beyond those of rest, diet and climate.—*Courtesy Biol. Absts.*

VELHAGEN, K.

Exophthalmos in the light of recent advances. *Deutsche med. Wchnschr.* 68: 81. 1942.

The condition of the orbit is maintained through a complex interaction of autonomic impulses and hormonal influences, part of the latter directly from the anterior pituitary and part indirectly from different glands including the antithyrotrophic or hormone. Exophthalmos results from disturbance of this equilibrium. Direct autonomic effects on the orbital muscles are of less importance than those received by the endocrine glands.—*Courtesy Biol. Absts.*



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## Testosterone Therapy of Male Eunuchoids

### V. Results from Methyl Testosterone Linguets

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IN A series of papers (1, 2, 3, 4) the principal author and several associates have contributed evidence establishing the clinical effectiveness of various testosterone compounds in the treatment of a highly specific endocrine deficiency, primary male hypogonadism or eunuchoidism. In successive reports the various modes of administering testosterone have been discussed and compared with regard to the convenience of dosage necessary to bring about improvement and the maintenance of the benefits achieved. These publications included convincing photographic (before and after treatment) proof that the intramuscular injection of testosterone propionate, the implantation of methyl testosterone pellets, the peroral swallowing of methyl testosterone tablets and the sublingual absorption of testosterone compounds dissolved in propylene glycol—all were successful in correcting the severe genital retardation of primary hypogonadism.

In the last paper of this group (4) testosterone propionate, methyl testosterone and

free testosterone, each dissolved in propylene glycol so that 0.2 cc. contained 5 mg., were administered sublingually in daily doses ranging from 10 to 25 mg. Six typical eunuchoids whose condition previously had been improved and who had been successfully maintained by parenteral, implantation, and/or oral administration of testosterone compounds, continued their improved states on sublingual testosterone. In only 1 of the 6 cases was the sublingual mode of therapy more economical in milligrams required than the peroral route. All of the patients preferred swallowing tablets to dropping a solution under the tongue.

Four hypogonadal patients who had not previously received any testosterone therapy derived striking benefits subjectively and objectively from the sublingual administration of testosterone compounds. Larger oral doses of methyl testosterone would have been required to initiate similar improvement. Sublingually, free testosterone was more effective than either methyl testosterone or testosterone propionate.

The present paper contains additional evidence of the effectiveness of therapy by the sublingual route. The new feature consists in

the use of highly compressed tablets, each containing 5 mg. of methyl testosterone.<sup>1</sup> As a rule this tablet was placed under the tongue and kept there until dissolved. This might require 15 to 30 minutes. The patient was instructed not to swallow or expectorate during this absorptive period. Some patients found it more convenient to place the tablet between the gum and the cheek, near the second molar. Several of the patients had had previous experience with the sublingual method when testosterone compounds had been dissolved in propylene glycol. All were unanimous in considering the compressed tablet a more convenient and pleasant tasting vehicle than the propylene glycol solution. An additional advantage was the higher potency of these linguets, since almost uniformly, a decidedly smaller daily dose sufficed to maintain their improved status. The only reference to linguet treatment with methyl testosterone in male hypogonadism which we have discovered is the single case report of Spence (5). The patient was a man, aged 23 years, who had been castrated in childhood. After initial heavy dosage of testosterone propionate parenterally, he had been maintained satisfactorily on a peroral dose of 15 mg. daily of methyl testosterone. Spence found that two 5 mg. methyl testosterone linguets daily maintained equal benefits.

Herewith follow the protocols of 12 cases. Six of the 12 cases included in this series have been reported in previous papers (1, 2, 4) in more elaborate detail. The patients in these 6 cases were characteristic examples of severe eunuchoidism which originated prior to the age of normal adolescence; they had been exceedingly immature at the ages of 24, 24, 31, 24, 29.5 and 21 years, respectively. Subsequently they had been treated with testosterone, administered parenterally or by implantation, by tablets perorally, or by solution sublingually. They had all been vastly improved and successfully maintained by means of one or more of these procedures. Since they had been observed for a sufficiently long period of time to permit critical comparative appraisal of parenteral, implantation, oral and sublingual ad-

ministration of testosterone compounds, we considered them excellent controls for a trial of methyl testosterone linguets.

The remaining 6 patients in this series represented several types of male hypogonadism. None of these cases, except *Case 12*, had been reported (6), and some of them had not received any form of testosterone therapy before. All of them displayed striking improvement from therapy with methyl testosterone linguets. No other treatment was given. We believe, therefore, that the benefits achieved may be properly ascribed to the administration of the methyl testosterone linguets.

#### CASE REPORTS

*Case 1; R.C. (U 57397).* *Case 7* in (1); *Case 1* in (2) with photographs; *Case 1* in (4). The patient was 24 years old when first seen in April, 1940. His appearance was characteristic of that of pre-adolescent eunuchoidism. He had typical disproportionately long extremities, shaved infrequently and had a high pitched voice. The pubic hair was scant and axillary growth was moderate. The penis was small (length 5 cm.); the testes were the size of small olive pits. The left testis was undescended. The prostate was barely palpable. The bone age was 16 to 17 years at 24 years of age.

Between April, 1940, and May, 1941, he had improved greatly with implantations of methyl testosterone, the dose varying from 143 to 800 mg. The stimulating effects of the individual implants lasted from 4.5 weeks to 5 months.

Between May, 1941, and April, 1942, the patient received either methyl testosterone, testosterone propionate, or free testosterone, dissolved in propylene glycol and administered sublingually in doses of 5 mg. four times daily. A survey of the 11 months of sublingual therapy showed that the patient had lost ground somewhat, more especially in the subjective sphere,<sup>2</sup> although the size of the external genitalia had not diminished.

In April, 1942, linguets were substituted, using methyl testosterone in compressed 5-mg. tablets

<sup>1</sup> These methyl testosterone linguets were furnished for this study by Ciba Pharmaceutical Products, Inc., Summit, N. J.

<sup>2</sup> As stated on page 634 in the paper by Escamilla and Lissner on "Testosterone Therapy of Eunuchoids," *J. Clinical Endocrinology* 1: 633, 1941: "The subjective changes consist of an increased feeling of well-being, better appetite, development of self-confidence, greater initiative, more energy and endurance, cheerfulness instead of moodiness, and optimism instead of depression. The patient is further encouraged by his ability to obtain a position or promotion in labor or business endeavors. Convincing also is the onset or markedly increased frequency of erections, the appearance of nocturnal emissions, and the desire to masturbate or seek sexual intercourse. Less conspicuous, but occasionally noted, is the disappearance of headaches and indigestion. Rarely, the incidence of convulsive seizures may be diminished."

times daily. During the succeeding 8 months, two attempts were made to reduce this dose to 10 or 15 mg. daily. The former dose of 20 mg. daily had to be resumed as on both trials of reduced dosage the hair growth seemed to stop, erections and libido diminished and weight was lost.

In this typical eunuchoid, four 5-mg. linguets of methyl testosterone daily maintained a satisfactory status, both subjectively and objectively. This dose is the same as that used when testosterone was dissolved in propylene glycol and administered sublingually, but 10 mg. less than when methyl testosterone tablets were used perorally.

It is noteworthy, also, that although this patient had received intensive testosterone treatment for two years prior to linguet therapy, the penile dimensions increased considerably during this latter regime (fig. A, B and C). These observations regarding linguet therapy covered a period of 10 months.

*Case 2, L. K. (U 20634). Case 3 in (1); Case 3 in (2) with photographs; Case 2 in (4).* The patient was 24 years old when first seen in September, 1937. He had disproportionately long arms and legs of a typical eunuchoid. He had never shaved and his voice was high pitched. The pubic hair was sparse and only a very few axillary hairs were present. The penis was small (length 4.75 cm.) and the scrotal content consisted of some questionable tissue in the left side. The bone age was 15 years at 24 years of age.

He was vastly improved by 16 months of parenteral administration of testosterone propionate, a total of 500 mg. In the following year (November, 1939, to November, 1940) the patient received 5 implants of methyl testosterone, the dosage ranging from 101.3 g to 164 mg. per implant. The previously attained improvement was adequately maintained, both subjectively and objectively. This was likewise accomplished between November, 1940, and May, 1941, by the peroral consumption of 30 mg. daily of methyl testosterone. Subsequently, between May, 1941, and April, 1942, his improved status was equally well maintained by one-half this amount, 15 mg. daily, administered as free testosterone dissolved in propylene glycol and absorbed sublingually.

In April, 1942, linguets were substituted, using methyl testosterone in compressed 5-mg. tablets, 5 mg. daily. In September, 1942, this dose was reduced to 10 mg. daily and this amount proved adequate to insure satisfactory intercourse once a week. The mentioned slight tenderness of the nipples. The size of the genitalia remained the same. He had noticed definite darkening of the beard. There was no change in body weight.

In this typical eunuchoid, two 5-mg. linguets of methyl testosterone daily maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 6 months.

*Case 3; J. J. (U 36521). Case 4 in (1) with photographs; Case 4 in (2); Case 4 in (4).* The patient was

31 years old when he was first seen in May, 1938. He had typical pre-adolescent eunuchoidism with disproportionately long extremities; the height was 71 in. and weight 123 lb. The voice was high-pitched, he had

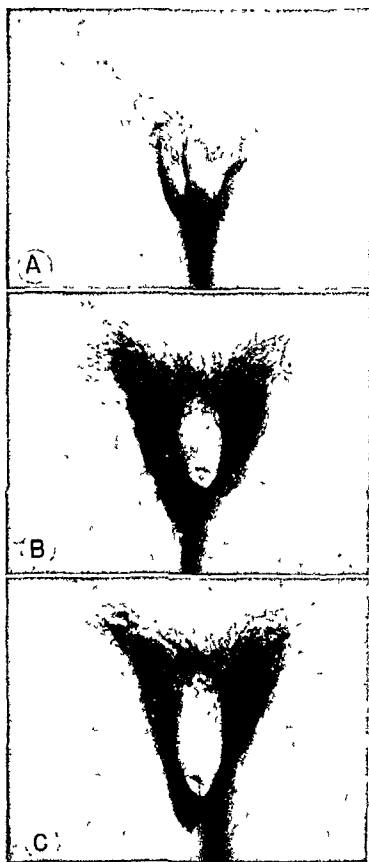


FIG. 1 PRE-ADOLESCENT EUNUCHOIDISM. *Case 1, R. C. Age 24 yr. A. April, 1940. B. January, 1943. Testosterone implants and sublingual testosterone therapy from April, 1940 to January, 1942. C. October, 1942. April to October, 1942, 4 linguets, 20 mg., of methyl testosterone daily.*

a few axillary hairs and a moderate amount of pubic hair. He clipped the fuzz from his face every 2 to 3 weeks. The penis was small (length 4.5 cm.). Testes and scrotum were very small, the prostate was not palpable. The bone age was 18 years at 31 years of age.

He was vastly improved by parenteral administration of testosterone propionate, receiving 3800 mg. between January, 1939, and February, 1940. These



benefits were maintained in the succeeding 9 months by 4 implants of methyl testosterone varying in size from 102.7 to 148.1 mg. Between November, 1940, and April, 1941, the improved status was continued by the peroral use of 30 mg. daily of methyl testosterone. Between April, 1941, and April, 1942, methyl testosterone, testosterone propionate and free testosterone, each dissolved in propylene glycol, were administered sublingually. In this patient, doses of 15 mg. daily, sublingually, were far less effective than 30 mg. perorally.

In April, 1942, linguets were substituted, using methyl testosterone in compressed 5-mg. tablets, 15 mg. daily. Subsequently, this dose was reduced to 10 mg. daily, and later to 5 mg. daily, and finally to 5 mg. every other day. This small amount, in the form of a linguet, maintained a satisfactory status, both subjectively and objectively, quite remarkably, considering the infantile condition of this typical eunuchoid at 31 years of age. These observations regarding linguet therapy covered a period of 7 months.

*Case 4; F.V. (U 62077).* *Case 6* in (2) with photographs; *Case 5* in (4). The patient was 24 years old when first seen in July, 1940. He had disproportionately long extremities and looked younger than his stated age. His voice was high-pitched, he had scant axillary and pubic hair and no beard or other body hair. The penis was small (length 4 cm.); the testes were small and soft; the prostate was about two-thirds normal size. The bone age was 16 years at 24 years of age.

In August, 1940, he received an implant of 117 mg. of methyl testosterone; in September, 1940, a second implant of 122.9 mg.; and in November, 1940, a third implant of 600 mg. The stimulating effects of this last implant had subsided entirely 11 weeks later. Between February and June, 1941, the status of the patient was successfully maintained by the peroral use of 30 mg. daily of methyl testosterone. Between June, 1941, and April, 1942, fairly satisfactory results were obtained from the sublingual administration daily of 15 mg. of free testosterone dissolved in propylene glycol.

In April, 1942, linguets were substituted using methyl testosterone in compressed 5-mg. tablets, 15 mg. daily. Subsequently, this dose was reduced to 10 mg. and later to 5 mg. daily. In this typical eunuchoid one 5-mg. linguet of methyl testosterone per day maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 6 months.

*Case 5; S.S. (U 72982).* *Case 8* in (4) with photographs. The patient was first seen on June 9, 1941, at the age of 29.5 years. He looked like an elderly boy. He had no beard. The pubic escutcheon was relatively sparse and of feminine type and the axillary hair was scant. The genitalia were infantile; the penis was tiny, measuring 2.5 cm. in length and 4.5 cm. in circumference; the scrotum was empty; the prostate was not palpable.

Between June, 1941, and April, 1942, he received testosterone compounds sublingually (dissolved in propylene glycol) in doses of only 12.5 mg. daily. Improvement, both subjectively and objectively, was remarkable, considering the relatively small dose and the fact that he had not received any other form of testosterone therapy prior to this. Previous experience in comparable cases of severe primary hypogonadism indicated that at least four times the amount daily would have been required to achieve equivalent improvement if the treatment had consisted of oral ingestion of methyl testosterone tablets.

In April, 1942, linguets were substituted using methyl testosterone in compressed 5-mg. tablets, 10 mg. daily. With this dosage the patient's voice became deeper and huskier and the hair growth in the axillae and on the arms and legs increased noticeably. The patient appeared more mature and behaved accordingly. Subsequently, the daily dose was reduced to one 5-mg. linguet daily, without diminishing the patient's weight, strength, or energy. However, he noted a decreased amount of ejaculate from masturbation.

In this typical 30-year-old eunuchoid, one 5-mg. linguet of methyl testosterone per day maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 10 months.

*Case 6; B.C. (U 4545).* *Case 6* in (1) with photographs; *Case 5* in (2); *Case 3* in (4). This patient was first seen in March, 1933, when he was 17 years old. He was a characteristic example of pre-adolescent eunuchoidism with small genitalia, complete absence of secondary sex manifestations and disproportionately long extremities. During the next 3.5 years various endocrine preparations were tried with negligible effect.

Between November, 1936, and November, 1939, he was vastly improved by parenteral administration of testosterone propionate, totalling, 10,250 mg. These benefits were maintained and enhanced in the succeeding 8 months by 3 implants varying in dosage from 109.6 to 138.3 mg. Between November, 1940, and April, 1941, the peroral administration of methyl testosterone in 10-mg. tablets, at first using 30 mg. daily, subsequently, 20 mg. daily and later, 10 mg. daily, sufficed to maintain him in a satisfactory condition. Between April, 1941, and April, 1942, methyl testosterone, testosterone propionate and free testosterone, each dissolved in propylene glycol, were administered sublingually. In this patient a sublingual dose of 10 mg. daily had an effect neither greater nor less than an oral dose of 10 mg.

For the succeeding 6 months this patient received no treatment whatsoever. For the first 3 months of this period, the sexual and general status remained unaltered. Gradually, during the next 3 months, the frequency of erections diminished and the penis decreased in size from 12.25 cm. to 10.5 cm. in length. He was instructed to try the effect of one 10-mg.

tablet daily of commercial methyl testosterone, placed under the tongue. Six weeks later he reported improvement and volunteered the belief that this dose absorbed sublingually was more potent than when swallowed. The penis had regained the former dimensions.

At this time he was instructed to substitute one 10-mg. linguet of methyl testosterone for the 10-mg. tablet. This dose proved equally effective.

*Case 7; D.N. (U 83782).* This patient, a 36-year-old man, was first seen on May 11, 1942. He com-

plained that the penis was about the size of a small olive. The penis measured 3.5 cm. long by 7 cm. in circumference (fig. 2, B). The B.M.R. was -7 per cent. The Kahn and Kolmer reactions were negative.

On May 14, 1942, administration of methyl testosterone in 5-mg. linguets, was started in a dosage of 20 mg. daily. By June 25, 1942, he was having 4 or 5 erections daily, which was very annoying. He had had one nocturnal emission and successful intercourse twice. The dosage was therefore reduced to 10 mg. daily. With this amount he had erections when stimu-

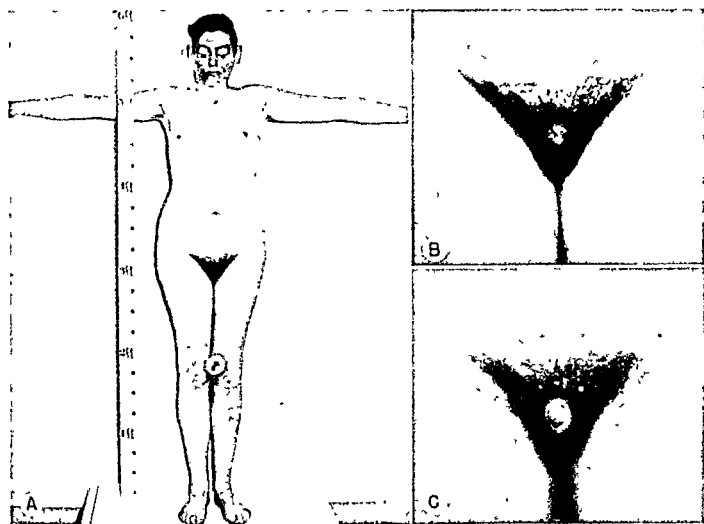


FIG. 2. PRE ADOLESCENT EUNUCHOIDISM *Case 7, D.N.* Age, 36 yr. A, B May, 1942. C November, 1942. Methyl testosterone linguets, 10-15 mg. daily from May, 1942, to November, 1942.

plained of lack of sexual development which had been untreated until March, 1941. Between March, 1941, and August, 1941, he had received 1000 mg. of testosterone propionate. This had been given in twice weekly injections of 25 mg. each, alternating with injections of an anterior pituitary preparation. On the days when he received no injection he took 20 mg. of methyl testosterone by mouth. This treatment produced deepening of the voice and growth of pubic and axillary hair.

The patient was 72.5 in. tall and weighed 188.5 lb. The span was 74 in. and the lower measurement was 38 in. from the pubis to the soles of the feet (fig. 2, A). His face was finely wrinkled, with a fawn colored complexion. Beard was practically non-existent. There was a well marked gynecomastia. The axillary hair was sparse, but the pubic escutcheon was heavy and female in distribution. The scrotum was small and retracted. Both testes were in the inguinal canals. Each testis

lated and held intercourse about every two weeks. On Nov. 19, 1942, the penis measured 5 cm. long by 8 cm. in circumference (fig. 2, C). At this time the dosage was increased to 15 mg. daily. When seen one month later, the patient felt much better on this increased dosage, and the improved sexual status was successfully maintained. These observations regarding linguet therapy covered a period of 9 months.

*Case 8; T.H. (U 88717).* This patient was first seen on Oct. 16, 1942, at the age of 19 years, 7 months. He complained of sexual impotence. His development and growth were normal until the age of 16.5 years. At the age of 13 years, one testicle became swollen for no apparent reason and was surgically drained. At the age of 16.5 years, a similar episode occurred involving the other testicle. Following the second attack, he noticed marked loss of strength, cessation of erections and emissions, and failure to develop further male charac-

teristics. About one year before admission to the clinic, he was given injections of testosterone propionate, 25 mg. twice a week, over a period of 3 months. During that time the patient gained weight and felt much stronger. His beard began to grow and he had daily erections, but no emissions. He had been untreated since January, 1942, and noted decreased energy, regression of his beard, cessation of erections, and a loss of 10 lb. in weight.

The patient was an asthenic boy with a moderately high-pitched voice. There was a rather marked, coarse, involuntary tremor of the hands. He was 68.25 in.

methyl testosterone using 5-mg. linguets, in a dose of 15 mg. daily.

After 6 weeks of therapy the patient had gained 13.5 lb. in weight and felt much more energetic. Erections were occurring every other day, but there had been no emissions nor inclination to masturbate. At this time the dose was reduced to two 5-mg. linguets daily.

One month later, Jan. 21, 1943, the patient reported fewer erections. However, he had continued to gain weight, an additional 7.5 lb., making a total of 21 lb. in a period of almost 10 weeks!

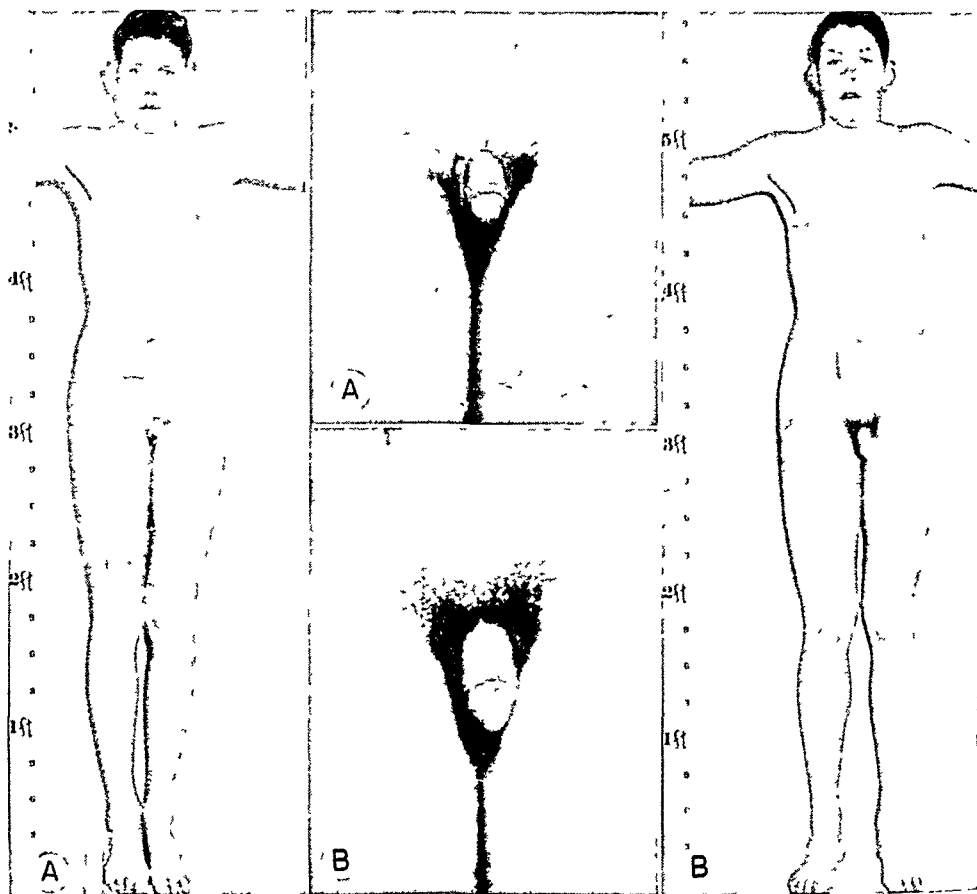


FIG. 3. PRE-ADOLESCENT EUNUCHOIDISM. Case 9, age 19 yr. 4 mo. A. November, 1942. B. February, 1943. Methyl testosterone linguets, 15 mg. daily. Gauze dressing covers recent appendectomy incision. Right side of pubic escutcheon shaved from November, 1942, to February, 1943.

tall and weighed 127.4 lb. His span was 68 in. and lower measurement, from pubis to soles, was 33.25 in. He had no beard, and the pubic escutcheon was feminine in type. The penis measured 8.5 cm. long and 8 cm. in circumference. Neither testis could be seen or felt; the prostate felt small and flat. Evidently the bilateral orchitis resulted in complete atrophy of both testes. His condition was classified as "post-adolescent post-infectious hypogonadism." However, the pubic hair had not dropped out and the penis had not shrunk to any marked extent. The B.M.R. was +13 per cent. The glucose tolerance was normal.

On Nov. 14, 1942, treatment was started with

Case 9; L.V. (U 89573). A boy 19 years and 4 months old, was first seen on Nov. 11, 1942. He complained of bilateral cryptorchidism and lack of sexual development. Four weeks before admission he underwent an operation for acute appendicitis. Otherwise his past history was negative.

The patient was 70.4 in. tall and weighed 133.75 lb. His span was 74.6 in. and the lower measurement was 38 in. from the pubis to the soles of the feet. There was no beard. Axillary and pubic hair was sparse and the pubic hair on the right side had recently been shaved for the appendectomy. The penis measured 4.5 cm. long by 6.5 cm. in circumference. The scrotum

small and retracted. No testes were palpable in scrotum or inguinal canals. The prostate was developed. The B.M.R. was +5 per cent; the age, 15 years, a retardation of about 4 years.

Nov. 12, 1942, administration of methyl testosterone in 5-mg. linguets was initiated using a dosage mg. daily. On Dec. 10, 1942, one month after

When last seen, Feb. 20, 1943, he weighed 159.25 lb., a total gain of 25.5 lb. in 3 5 months! During this same period he grew 7/8 in. (fig. 3, A). The remarkable growth of the penis and pubic hair is apparent in figure 3, B.

Case 10; J.F. (U 80642). This patient was first

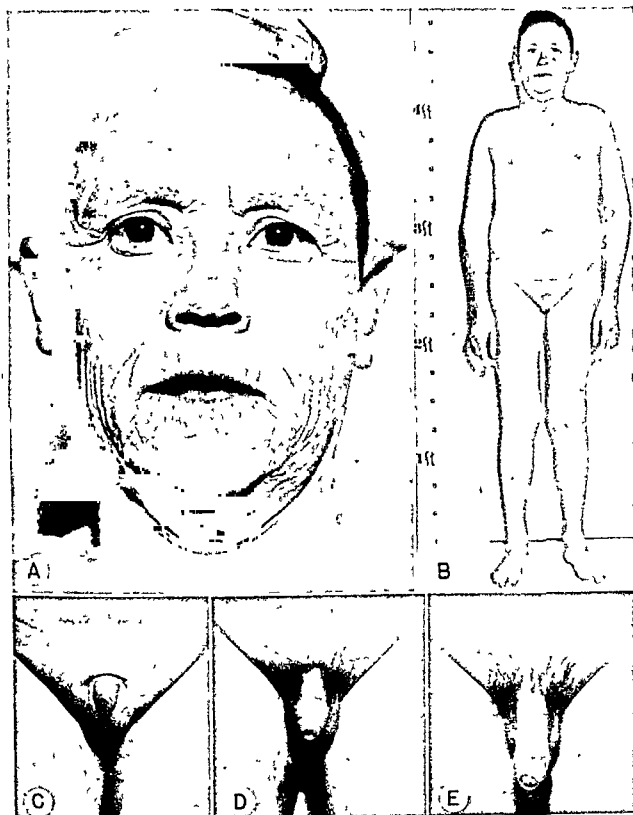


FIG. 4. PRIMARY HYPOGONADISM WITH SHORT STATURE Case 10, J.F. Age, 43 yr A, B, C January, 1942 Methyl testosterone, 10-mg tablets perorally, 100 mg daily D, June, 1942 E October, 1942 Methyl testosterone, 5 mg linguets, originally 25 mg daily, gradually reduced to 5 mg daily from June, 1942, to October, 1942

ing therapy, the patient weighed 145.25 lb, this a gain of 11.5 lb. One month later, on Jan. 7, he had gained an additional 8 5 lb, weighing 5 lb. Erections occurred two or three times daily he penis measured 9 cm. long by 10 cm. in circumference. In general he felt much stronger and more jetic. The testes could not be felt.

seen on Jan. 29, 1942, at the age of 43 years, 5 months He complained of lack of skeletal growth and failure to develop secondary sexual characteristics. He was born in Russia and had always had good health. He had never had any facial or pubic hair and only very little axillary hair. Occasionally he experienced erections when he thought about women or took hot

showers, but he had never had intercourse or masturbated and had had no nocturnal emissions.

The other members of his family were of average size and developed normally except for a brother two years older who was suffering from the same conditions as the patient.

The patient was a short man (height 58.25 in.) looking considerably older than his stated age. His face was deeply wrinkled and beardless (fig. 4, A and B). The skin was fine textured and dry. The hair was fine and normally oily. The weight was 102.25 lb.; span, 62.25 in.; the lower measurement from pubis to soles, 30.75 in. There was no pubic hair and the axillary hair was very sparse. The penis measured 3.5 cm. long by 4.75 cm. in circumference (fig. 4, C). The testes were of lima-bean size and retracted easily into the inguinal canals. The prostate could not be palpated. The B.M.R. was -12 per cent. The bone age was 16 years at 43 years of age. Urine creatine, none; urine creatinine, 790 mg.

Oral methyl testosterone therapy was started Feb. 12, 1942, in a dosage of 100 mg. daily. After 3 days of treatment erections occurred 6 or 7 times daily, but no emissions. On June 24, 1942, after 4.5 months on this dosage, the patient weighed 109.25 lb., a gain of 7 lb. His voice was much deeper, and considerable pubic hair had appeared. The scrotum was more relaxed and corrugated. The penile measurements had increased from 3.5 cm. and 4.75 cm. to 7 cm. in length and 8 cm. in circumference (fig. 4, D). The prostate could now be palpated as a definite organ about 2 cm. in diameter.

At that time, June 24, 1942, treatment was changed to methyl testosterone in 5-mg. linguets using 25 mg. daily. By July 9, 1942, there had been no subjective change on this markedly reduced dosage, and the penis measured 8 cm. long by 8.5 cm. in circumference. Erections continued 4 or 5 times daily. Therefore, the dosage was reduced to 3 linguets, 15 mg. daily. After 2 months on this dosage, the erections had decreased to 2 or 3 daily, but the pubic hair growth had increased. On Sept. 9, 1942, the dose was again reduced, to 2 linguets, 10 mg. daily. The penis and pubic hair continued to grow as is evident in figure 4, E, taken in October, 1942. Since there was no change for the worse after 5 weeks on this dosage, it was further reduced to 1 linguet, 5 mg. daily. On this small amount erections decreased to 2 or 3 times a week, but there was no loss of general strength or energy. On Jan. 28, 1943, the weight had decreased to 106 lb. The penis measured 7.5 cm. long by 9 cm. in circumference. During the year of testosterone therapy the patient grew 3/8 in. despite his age of 43 years.

*Case 11; A.R. (U 85578).* A 73-year-old man was first seen on July 16, 1942. He complained of hot flushes, melancholia, nervousness, emotional instability with frequent weeping spells, ankle edema and marked decrease in mental activity and ability. One year previously bilateral orchidectomy had been performed because of an injury to the scrotum and testes.

Within 2 days after the operation, all of the above symptoms began to appear. He noticed, also, that the pubic hair failed to grow as vigorously as previously and he became more sensitive to cold. Libido decreased, although partial erections still occurred once or twice a week. His weight increased from 176 to 183 lb. and the fat was distributed about the abdomen more than ever before. The hot flushes were usually precipitated by exertion, or any type of emotion. They lasted about 2 minutes and occurred from 20 to 40 times daily.

He had always been energetic and alert mentally, as an actor, author and playwright, but since castration had lost all ambition, zest and ability to concentrate.

The patient looked several years younger than his stated age of 73 years. He was quite emotional and occasionally burst into tears during the interview and examination. There was a loud, rasping systolic murmur over the apex of the heart, transmitted to the axilla and to the base of the heart. The blood pressure was 175/85 mm. Hg. Both testes were surgically absent. There was a left, direct, inguinal hernia. Marked edema of the feet and ankles extended 2/3 of the distance upward to the knees. Blood and spinal fluid Wassermann reactions were positive.

On July 16, 1942, he was given digitalis, 0.2 gram daily, and phenobarbital, 0.03 gram twice daily. On Aug. 6, 1942, he was having some nausea and visual disturbance, but the therapy was continued. In addition, testosterone propionate hypodermically was started in a dosage of 25 mg. once a week. He received 5 such injections and felt some better. However, his 'climacteric' symptoms would recur before the week had elapsed between injections.

On Sept. 3, 1942, he was given one 5-mg. linguet of methyl testosterone daily, and the injections were discontinued. The digitalis and other cardiac therapy was maintained, plus mercupurin, in spite of nausea. By Oct. 1, 1942, the melancholia had practically vanished and he had no more hot flushes.

Because of several favorable reports (7, 8, 9, 10) in recent medical journals regarding male hormone therapy in older men suffering from cardiovascular ailments, it was deemed opportune to test the cardiovascular effectiveness of testosterone therapy in this patient by confining treatment entirely to administration of methyl testosterone linguets. Accordingly, on Oct. 1, 1942, treatment with digitalis, mercupurin, and phenobarbital, were suspended.

At the end of 3 weeks of therapy with methyl testosterone linguets only the ankle edema was almost entirely gone, the pulse was normal and regular, he was no longer having hot flushes, his mental activity was almost normal, and he was not emotional or melancholic. On Dec. 17, 1942, he was still noticing some ankle edema when on his feet a long time. The dyspnea had diminished markedly. Erections occurred practically every morning and he had erotic dreams about once a week.

On Jan. 7, 1943, the patient reported some war-

effects of therapy with some return of the hot flashes. Consequently, the dose was increased to two mg linguets, 10 mg, daily. Three weeks later the patient reported that with the increased dosage the flashes had ceased almost immediately, the melancholia vanished, and that there was a decrease in apnea, dyspnea and nocturia. However, the ankle edema had increased somewhat.

*Case 12; K K (U 70442), (6)* with photographs of his patient was first seen in March, 1941, when 15 years old. His condition was recognized as acroegaly of about 4 years' duration. Gradual, and finally, total loss of libido and potentia had developed between October, 1940, and March, 1941, some diminution in the size of the genitalia had been noted by the patient.

During April and June, 1941, two courses of pituitary irradiation were administered consisting of 1800 and 2700 roentgens, respectively. The benefits derived were manifested by disappearance of somnolence, chary, polyuria, polydipsia, polyphagia and headaches, plus improvement of visual acuity and restoration of normal visual fields. However, the patient's strength and energy were still below par and libido and potentia remained absent.

In view of the remarkable results achieved in the rehabilitation of eunuchoids by testosterone therapy, and because experimental work (11, 12, 13) suggested that such treatment might inhibit the hyperactivity of an anterior pituitary adenoma, testosterone propionate was given parenterally in 25 mg doses three times a week for 3 months, the total dose being 850 mg. The improvement was dramatic, libido and potentia were restored completely, and strength and vigor had returned so that the patient was able to resume his occupation as a roofing estimator. Subsequently, his improved status was maintained by methyl testosterone orally in doses of 40 mg daily, and later 20 mg daily.

On June 25, 1942, therapy was started using two 5-mg linguets of methyl testosterone daily. Subsequently, this dose was increased to 15 mg daily and proved adequate for the following 4 months. On January 1, 1943, the patient volunteered the observation that he felt better when taking 15 mg daily of methyl testosterone in linguets than with 30 mg daily perorally.

#### SUMMARY OF CASES AND DISCUSSION

The purpose of this investigation was to determine whether highly compressed tablets of methyl testosterone, designed for slow sublingual absorption, would: a), maintain the improvement previously produced and maintained in cases of severe eunuchoidism by administration of testosterone propionate intramuscularly, by implantation of methyl testos-

terone pellets subcutaneously, by administration of methyl testosterone tablets perorally and/or by the sublingual absorption of testosterone dissolved in propylene glycol, b), initiate an improved sexual status subjectively and objectively in hypogonadal individuals who had not previously received any form of testosterone therapy, c), reveal the advantages or disadvantages, economically and otherwise of the use of linguets as compared to parenteral, implantation, peroral, or the absorption sublingually of a testosterone solution. We believe that our experience in the 12 cases reported provides an adequate answer to these three considerations.

The effectiveness of methyl testosterone linguets as a maintenance regime was tested in 7 patients, all of whom had been typical examples of severe pre-adolescent eunuchoidism and who had been exceedingly immature at the ages of 24, 24, 31, 24, 29, 5, 21, and 35 years, respectively. At the time methyl testosterone therapy in the form of linguets was initiated they had been vastly improved by other forms of testosterone therapy. They had reached the ages of 26, 29, 35, 26, 30, 26, and 36 years, respectively.

In *case 1*, the patient progressed satisfactorily using 20 mg of testosterone linguets daily, an amount equivalent to that which was effective when administered sublingually in propylene glycol, but which was 10 mg. less than the amount required when methyl testosterone tablets were swallowed. However, further genital development occurred despite 26 years of age, previous testosterone implants and sublingual therapy (fig 1, B and C).

In *case 2*, the patient maintained a satisfactory status, both subjectively and objectively, on two 5-mg linguets of methyl testosterone, as compared to 15 mg daily sublingually when the propylene glycol solution was employed, and 30 mg daily when methyl testosterone tablets were swallowed.

In *case 3*, the patient, originally an example of a very severe primary gonadal deficiency, was maintained satisfactorily on one 5-mg linguet of methyl testosterone daily. This small dose was more effective than 15 mg. daily when testosterone was dissolved in propylene glycol and absorbed sublingually and matched the good

effects of 30 mg. perorally. In this patient linguet therapy constituted a notably economic method.

In *case 4*, the patient, another typical eunuchoid, derived equivalent maintenance benefit from only one 5-mg. linguet of methyl testosterone as compared to the need of 15 mg. daily when testosterone dissolved in propylene glycol was administered sublingually, and the results equaled those obtained previously from 30 mg. daily perorally; again a remarkable saving in medication.

In *case 5*, the patient had been greatly improved and well maintained on 12.5 mg. daily of free testosterone dissolved in propylene glycol and absorbed sublingually. Equally excellent results were obtained by one 5-mg. linguet of methyl testosterone daily; again an appreciable saving of material.

In *case 6*, the patient had been satisfactorily maintained on one 10-mg. tablet perorally, and likewise on 10-mg. daily absorbed sublingually (free testosterone dissolved in propylene glycol). One 5-mg. linguet daily accomplished the same purpose.

In *case 7*, prior to coming under our observation, the patient had been greatly improved by injections twice a week of 25 mg. of testosterone propionate plus 20 mg. of methyl testosterone daily three times a week perorally. He had been without any treatment for 9 months when we instituted therapy with methyl testosterone linguets. Only three 5-mg. linguets, 15 mg. daily, were required to obtain further improvement (fig. 2, *B* and *C*).

In *case 8*, a lad almost 20 years old who had suffered destruction of both testes from orchitis, one side at 13 years of age, the other at 16.5 years, had matured partially during the interim. He received testosterone propionate parentally for 3 months when 18 years of age, but this therapy had to be discontinued for economic reasons. He had been untreated for 10 months when therapy with methyl testosterone linguets was instituted in a dosage of 15 mg. daily. This amount produced a gain of 21 lb. in body weight in 10 weeks.

In *case 9*, the patient, a characteristic example of severe pre-adolescent eunuchoidism, had never received any form of testosterone

treatment. Therapy with methyl testosterone linguets was begun Nov. 12, 1942, and at time of this report, 3.5 months later, he had gained 25.5 lb., erections were occurring 2-3 times daily, and the penis and scrotum, as apparent in the photographs (fig. 3, *C* and *D*), had developed strikingly. This remarkable result was accomplished with but 3 linguets, 15 mg. daily. In view of reports such as that of Eidelsberg and Madoff (14) that as much as 100 to 150 mg. daily of methyl testosterone orally was necessary to produce similar improvement, it is clear that therapy with methyl testosterone linguets constitutes a very substantial saving.

In *case 10*, which represents an extraordinary instance of severe sexual retardation at the advanced age of 43 years, the patient received 100 mg. daily of methyl testosterone perorally for 4.5 months. Gratifying improvement is evident from the photographs (fig. 4, *C* and *D*). To determine what dosage of methyl testosterone linguets would maintain and perhaps further this improvement, an initial amount of 5 linguets, 25 mg. daily, was tried. Two weeks later this was reduced to 15 mg. daily; 2 months later to 10 mg. daily; and 5 weeks later to 5 mg. daily. The photograph (fig. 4, *E*) reveals that despite the sharp curtailment in dosage, the penis had enlarged appreciably and pubic hair had continued to grow. On this relatively tiny dose erections decreased in frequency, but there was no loss of strength and energy and the patient expressed himself as quite content. Here again an amazingly small dose proved satisfactory.

In *case 11*, the patient, a 73-year-old man, was castrated a year before because of trauma to the testes and had suffered severely from the climacteric symptoms of frequent hot flushes, melancholia, emotional instability with weeping spells and marked diminution in mental vigor and initiative. He received a total of 5 injections of testosterone propionate, given once a week. However, the climacteric symptoms persisted before the week had elapsed between injections. One to two 5-mg. linguets of methyl testosterone daily completely controlled the above symptoms and his mental alertness returned sufficiently to enable him to resume his

ensive reading and writing (as an author) here again a remarkably small dose was entirely satisfactory despite castration

Case 12 is that of a young acromegalic who suffered from secondary hypogonadism with complete loss of libido and potentia Testosterone propionate, parenterally, 25 mg three times a week for 3 months, restored his sexual vigor completely Subsequently, this improvement was maintained by three 5-mg linguets of methyl testosterone daily

#### SUMMARY

Twelve males, whose ages ranged from 19 to 73 years, were victims of severe hypogonadism Nine of these 12 patients had never matured, one had matured partially, one suffered from testicular deficiency secondary to acromegaly, one had been castrated at 72 years of age Some of these patients had been treated previously by other modes of testosterone therapy All were well maintained on much smaller amounts of testosterone compounds when methyl testosterone was administered in the form of 5 mg linguets designed for sublingual absorption In 6 of the 12 patients, one 5-mg linguet daily sufficed for maintenance a remarkably small dose Only 15 mg daily of methyl testosterone in linguets produced striking genital improvement in a 19-year old lad suffering from severe eunuchoidism and who had never had any other form of testosterone therapy He gained 25.5 lb in 3.5 months

Methyl testosterone linguets in the form of 5 mg hard compressed tablets for sublingual absorption, is to date, by far the most economical mode of administering androgens to

hypogonad males These linguets dissolve, and therefore absorb, slowly, about 15 to 30 minutes being required, patients do not find them unpleasant

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# Effect of Injections of Testosterone Propionate on a Male Subject with Nephrotic Syndrome<sup>1</sup>

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DURING the active phase of the chronic nephrotic syndrome loss of protein in the urine is a factor in lowering the plasma proteins to the edema level (1). Another possible cause is partial failure of albumin production (2). Careful attention to dietary protein and caloric intake, when supplemented by judicious restriction of salt and water, may do much to improve general nutrition (3-6) and control edema. Such measures are not very effective in maintaining an adequate level of plasma albumin but do offset serious inroads on tissue proteins.

In seeking for more active stimulation of the protein anabolism of these individuals, one's attention is naturally drawn to certain remarkable effects of some of the androgenic steroids. It is now a well-established fact that testosterone acetate or propionate will cause retention of considerable amounts of nitrogen in the dog (7,8) and also in man (9-12). In some experiments of our own (unpublished data) this effect has continued for as long as 80 days and the retention of nitrogen has been much greater than could be accounted for on the basis of hypertrophy of genital tissues. There are, in addition to nitrogen retention, renal changes noted, particularly in the mouse (13,14,15) and also reported in the rat (16,17,18). The renal tubular epithelium hypertrophies and the kid-

neys increase in weight in the mouse. Wells *et al.*, (19) found the diodrast  $T_m$  of young male dogs increased by as much as 100 per cent when large doses of testosterone propionate were injected. Selye (20) thought that administration of testosterone afforded partial protection to the kidneys of mice poisoned with bichloride of mercury. The suggestion that this form of hormonal therapy might prove beneficial in human renal disease has been made several times (16,20,21). At present it seems to have been tried but once and with negative results (18).

Although anatomical changes in the tubules are characteristic of the nephrotic state, and the usual tests of glomerular function are but moderately impaired, it would seem that serious lesions of the glomerular filter must exist otherwise proteins should not pass freely into the urine. From what is known of the effect of androgens on the kidney, one would be led to surmise, then, that they would not materially affect proteinuria unless indirectly by increasing the efficiency with which dietary protein was used to synthesize plasma protein. However, except in regard to nitrogen-retaining properties, there is little point in comparing the human and animal experiments, for the dosage that has been used to produce renal hypertrophy in animals is enormously greater on a per kg. basis than has been given to man.

The following case report deals with our experience in the treatment of the nephrotic state with testosterone propionate.

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## CASE HISTORY

A male, aged 24 years, was well until January, 1941, when he had a rather protracted respiratory infection consisting of sore throat, laryngitis and bronchitis. On recovery he felt well until June, 1941. The onset of symptoms at this time was insidious with weakness, mild anemia and swelling of ankles. The urine was found to contain large amounts of protein and many hyalin and granular casts with never more than an occasional erythrocyte. Blood: R B C 4.1 million/cu. mm, Hb, 13.4 gm per 100 cc. Serum: Total protein, 4.1 gm per 100 cc, albumin, 1.2 gm; globulin 2.9 gm, nonprotein nitrogen, 38 mg per cent, calcium, 7.1 mg per cent, inorganic phosphorus, 4.6 mg per cent. The serum was intensely lipemic at all times.

*Plasma Lipid*

Total lipid	2201 mg per cent
Phospholipid	464 mg per cent
Total cholesterol	977 mg per cent

*Urea Clearance*

Date	Clearance
7/23/41	Standard 60 per cent of normal
5/25/42	Standard 30 per cent of normal (Followed streptococcal cellulitis)
9/22/42	Maximum 69 per cent of normal
10/13/42	Standard 56 per cent of normal
2/1/43	Standard 48 per cent of normal
2/11/43	Standard 45 per cent of normal
3/4/43	Standard 46 per cent of normal

The patient's course was characterized by moderate edema at all times interspersed with episodes of severe generalized anasarca. One of the latter was observed on the metabolic service and appeared to have been due to marked increase in proteinuria following extraction of an infected tooth combined with simultaneous restriction of protein in the diet. In May, 1942, anasarca disappeared rapidly with a loss of 23 kg in weight following a cellulitis of the leg due to infection with hemolytic streptococcus. Proteinuria decreased markedly and the albumin fraction of the serum protein rose to 2.9 gm per 100 cc. As noted above, the urea clearance reached its lowest level at that time. Three months later, renal function, as measured by the urea clearance, had improved, proteinuria was again extremely high, the serum albumin lower, and the edema was increasing.

*Metabolic study*

The period of observation on testosterone propionate was one in which the patient was free from complicating illness and was able to cooperate fully.

*Method.* The subject lived on the metabolic ward where he received a constant and carefully weighed diet of 3170 calories and 125 gm. of protein per diem. The nitrogen content of

the diet was determined by macro-Kjeldahl analysis of composite samples of the daily food. Urine was collected in 24-hr. periods and analyzed for total nitrogen and total protein. Feces were marked with carmine and pooled in 5-day periods before analyses were made for nitrogen. Nitrogen balance was computed every 5 days. Vena punctures were performed without stasis in the morning, about 14 hours after the last previous meal and while the patient was still recumbent. Serum proteins were determined by the method of Howe.

Salt intake was estimated to be 2.5 to 3 gm. a day; liquids in the diet including drinking water were restricted to 1100 cc/day. The first three periods, 8 to 10, and the last six, 19 to 24, served as controls. Injections of testosterone propionate<sup>2</sup> were given intramuscularly in periods 11 to 18. The dose of hormone was 25 mg/day for 15 days, was increased to 50 mg/day for 15 days and then reduced to the initial level of 25 mg/day for 10 days. The total dose was 1375 mg in 40 days.

## RESULTS

Tabular and graphic presentations of the data appear in tables 1 and 2 and figure 1.

*Pre-treatment control period.* The subject was in moderately positive nitrogen balance during the preliminary control periods 8 to 10. During a previous admission, with a slightly lower protein intake, it had been impossible to prevent accumulation of edema without the administration of ammonium chloride and this was given in doses of 8 grams per day during periods 8 and 9. A diuresis resulted, accompanied by rather rapidly increasing proteinuria (22) and weight loss. With omission of the ammonium chloride in period 10 the proteinuria decreased and both this and the weight reached a fairly constant state.

*Testosterone treatment periods.* a) Nitrogen retention was above that of control periods due to injections of testosterone propionate in periods 11 to 18. The maximum effect was observed at the dosage level of 50 mg./day but the gain over that of 25 mg/day was small. The peak of retention appeared in period 15.

<sup>2</sup> Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, supplied the testosterone propionate (Perandren) used in this work.

TABLE 1. METABOLIC STUDY OF MALE SUBJECT WITH NEPHROTIC SYNDROME BEFORE, DURING AND AFTER TREATMENT WITH TESTOSTERONE PROPIONATE

Periods 5-Days	Nitrogen Balance	Urine Protein	Crea- tine	Creati- nine	Testos- terone Propi- onate	Body Weight
	gm.	gm.	gm.	gm.	mg.	lb.
8	+ 9.78	115.68	0.91	9.01		772.6
9	+ 7.24	154.00	1.17	8.59		73.55
10	+10.37	123.75	1.20	8.36		76.18
11	+16.83	142.60	0.69	8.64	125	77.31
12	+16.37	151.30	0.88	9.11	125	78.93
13	+17.92	151.10	0.82	8.48	125	80.29
14	+20.71	149.60	0.78	9.61	250	81.55
15	+20.24	146.90	0.74	9.25	250	83.16
16	+17.10	157.50	1.32	9.08	250	84.01
17	+16.23	159.40	1.11	9.50	125	84.40
18	+15.13	141.20	1.24	9.76	125	85.01
19	+10.04	165.30	0.97	10.20		84.72
20	+ 3.33	177.60	1.29	10.07		83.51
21	+ 3.92	157.30	1.15	9.49		84.16
22	+ 7.39	129.80	1.07	11.44		82.45
23	+16.36	123.25	1.17	9.93		78.06
24	+11.88	119.50	1.13	9.91		75.38 74.11

and thereafter the nitrogen retaining effect of the hormone seemed to decline slowly. There was a 'rebound' in urinary nitrogen when the hormone was withdrawn, but not of sufficient magnitude to produce a negative nitrogen balance. The average nitrogen retention per diem of control *periods 8 to 10* and *23 to 24* was 2.22 gm. The mean nitrogen retention in the periods of treatment with testosterone was 1.29 gm./day higher.

b) Proteinuria was exceptionally high at all times. There were many days during which the urinary protein was more concentrated than the protein of the serum. The increased proteinuria of *period 9* was probably caused by the action of the ammonium chloride (22). The highest values for urinary protein were found in the periods immediately following discontinuance of testosterone (*periods 19-21*). In neither instance was there any clear relationship between the amount of protein excreted and the volume of the urine. As mentioned in paragraph a), the periods considered to be free from testosterone effects were *8 to 10* and *23 to 24*. The mean proteinuria of these periods was less by 4.6 gm./day than that of the testosterone treatment periods (*11-18*). The increase in the latter, while not very great, has a probability of more than 100:1 of being real and not a purely chance observation.

c) *Gain in weight.* The increase in weight directly associated with therapy was 7.8 kg. Some of this was quite obviously the result of increasing edema. From the nitrogen balance (*periods 11-18*), one may estimate that 4.1 kg. was presumably muscle tissue. The remaining 3.7 kg. was extracellular water. Subjectively the patient felt stronger in spite of increasing edema, an observation directly opposite to his usual reaction when gaining rapidly in weight.

If the entire retention of nitrogen of the 8 experimental days is taken into account, one may calculate a gain in muscle tissue of 6.5 kg. This was completely obscured by the diuresis and loss of edema fluid which took place in *periods 21 to 24*.

d) The urea clearance did not change significantly during the periods of treatment.

e) Creatinuria was present in moderate degree and decreased somewhat during the first five periods of treatment.

*Post-testosterone treatment period.* The most interesting feature of this phase was the onset

TABLE 2. PROTEIN METABOLISM IN MALE SUBJECT WITH NEPHROTIC SYNDROME

Control Periods 8 to 10 and 23 to 24 (25 days)		
Protein intake from food		3125 gm
Protein lost in urine	636 gm.	
Protein deposited as tissue	347 gm.	
Sum of urine and tissue protein	983 gm.	983 gm.
Balance catabolized		2142 gm
Dietary protein converted to body protein		31.5%
Dietary protein wasted as urine protein		20.3%
Testosterone treatment periods 11 to 18 (40 days)		
Protein intake from food		5000 gm
Protein lost in urine	1200 gm.	
Protein deposited as tissue	878 gm.	
Sum of urine and tissue protein	2078 gm.	2078 gm
Balance catabolized		2922 gm
Dietary protein converted to body protein		41.5%
Dietary protein wasted as urine protein		24.0%
Entire experimental period (85 days)		
Protein intake from food		10,625 gm
Protein lost in urine	2589 gm.	
Protein deposited as tissue	1377 gm.	
Sum of urine and tissue protein	3966 gm.	3966 gm
Balance catabolized		6659 gm
Dietary protein converted to body protein		36.5%
Dietary protein wasted as urine protein		24.3%

a prolonged diuresis and a loss of 10 kg. in eight which began about 12 days after the hormone treatment was stopped. We would like to think that the following factors were contributory: a) A small but definite rise in serum protein from 3.0 to 3.8 gm./100 cc. Withdrawal of the salt and water-retaining effect of testosterone. c) Repair of depleted tissue protein, 'increased tissue turgor.' On the

## DISCUSSION

It is evident that testosterone propionate exerts its usual anabolic effect on protein metabolism in the nephrotic subject. Pre-treatment determinations of the excretion of 17-ketosteroids by our patient were made but were not considered very accurate due to the high concentration of urinary protein. Values of 14 to 15 mg. per day were obtained and

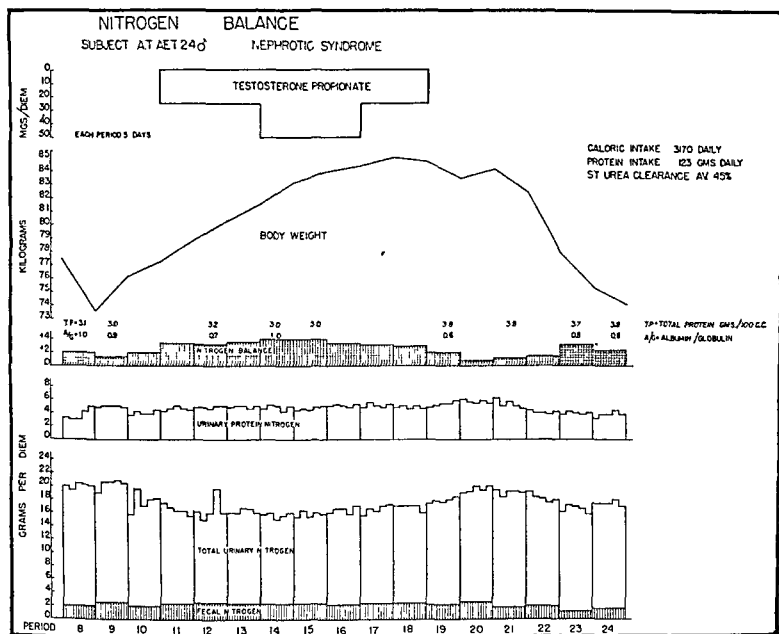


FIG. 1 Effect of injections of testosterone propionate on nitrogen balance, urinary protein nitrogen and body weight

her hand, such periods of diuresis have been observed in this type of patient without any demonstrable cause and this fact must be kept in mind in the assessment of any therapeutic results.

**Utilization of dietary protein to build body protein.** The ability of the patient to tolerate extremely severe proteinuria and deposit protein in his tissues simultaneously indicates an efficient utilization of dietary protein. This is revealed in the summary of the protein metabolism in table 2.

appear to indicate an adequate production of natural androgens.

The chief disadvantage to this form of therapy, but not a serious obstacle in the present instance, was its effect on retention of salt and water. Kenyon (9, 10, 12) has noted the electrolyte-retaining action of the hormone in man on several occasions. Its behavior in this respect appears to be exaggerated in nephrosis and might prove to be a source of embarrassment in a patient who was already seriously edematous.

The conversion of dietary protein to body protein (tissue and urine protein) was remarkably good and achieved the rather high level of 41.5 per cent of the intake in the periods of treatment with testosterone. Of the extra nitrogen utilized for formation of protein in these periods, about half seems to have contributed to a more intense proteinuria while the remainder was retained in the body. Both the increase in proteinuria and the small rise in concentration of serum protein suggest some increase in the synthesis of plasma proteins. More evidence on this point is required, however, in view of the rapid and sometimes inexplicable variations that occur in the urinary and plasma proteins of the nephrotic.

#### SUMMARY

An anabolic effect of injections of testosterone propionate on the protein metabolism of a nephrotic subject has been demonstrated. The hormone increases the rate of deposition of protein in the tissues and appears to augment proteinuria slightly. There is likewise a distinct tendency for edema to increase during the period of injections, presumably due to retention of salt and water.

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# Endocrine Treatment of Enuresis

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ENURESIS in the child is a condition which may have organic or psychogenic factors as a cause. The organic cause may be purely local and may consist of some palpable physical irritating stimulus, such as inflammatory conditions in the genito-urinary tract. It may be of a general physical nature such as that debility from nutritional causes or following severe illnesses. There may be endocrine disharmony with its influence on neuromuscular function. It may be entirely neurogenic due to organic disease and dysfunction or aplasia of either central or local, of nerve structures which innervate the bladder. The cause may be entirely psychogenic. The hypersensitive neuro-labile child with great neuro-instability or the psychopathic child with behavior complexes presents this type of case. Many believe that this type of etiology is predominant in all enuretics. The enuretic is an individual whose uro-muscular micturition mechanism is not normally stabilized. Many factors which do not affect the normal child act as adverse stimuli in the susceptible incontinent child.

Ederer and Lederer (1) believe that in all enuretics in whom the etiology is not on an organic or anatomic basis, loss or dislocation of the conditioned reflex is the real cause of the enuresis, and is of central nervous system origin. Excitability of the cortical cells is either increased or that of the sub-cortical cells is decreased, or both factors may be present. It is of course conceivable that in this concept of the etiology all kinds of local or environmental factors may contribute to the development of the central disorder.

The treatment of the condition is shaped largely according to the predominant etiologi-

cal factor and basically aims at the re-establishment and proper synchronization of the conditioned reflex. The desire to urinate must chronologically synchronize and coincide with the conscious action of the bladder sphincter-closing mechanism. Restriction of fluid intake, dietary changes and environmental changes which will influence and improve both the physical state and the psyche of the child are important curative measures. Re-education and re-establishment of an adequate conditioned reflex are the goal of any form of treatment.

Of a large list of drugs used the most useful have been atropine and the belladonna preparations. Recently ephedrine has been quite extensively used, not to control the enuresis, but to prevent the deep sleep which is often characteristic of the chronic enuretic, thus allowing him to awaken when the pressure in the bladder prompts the desire to urinate; this in turn initiates the conditioned reflex which sets in motion the mechanism of sphincter control.

The extensive research in the past decade or two in the field of endocrinology, the isolation of individual hormones, and discovery of their potent effects particularly on the sex glands and the sex organs, has led to some interesting observations and therapeutic experiences. The question has frequently been raised whether endocrine influences are not, among other things, a factor in the development of enuresis—the theory being advanced that immaturity of the genital structures and organs both as to muscular structure and urine control could be at fault. This view has been strengthened by some clinical reports which have appeared from time to time and which showed that the use of various endocrine substances seemed to have a

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definite effect in controlling or relieving the disorder.

Cain (2,3) used anterior pituitary products given orally and claimed good results for them in cases of incontinence. Nittis (4) found such preparations useful and effective in the treatment of enuresis in children. He proposes the acceptance of the theory that lack of maturation of the structures of the genito-urinary region is responsible for much of the nocturnal incontinence in many children and that the use of endocrine substances which are known to produce precocious maturity of the genital organs will prove beneficial. Malavozos (5), believing the underlying cause of enuresis to be immaturity of the genito-urinary organs, treated the condition with anterior pituitary substances with good result. Later he and Goldman (6) attempted to determine whether the follicle-stimulating or the luteinizing factor is responsible for the result and reached the conclusion that the best results are obtained only when both substances are given in fairly large doses. Huffman (7), accepting the theory that in most cases of nocturnal urinary incontinence in children the underlying cause is some form of immaturity of the structures responsible for micturition, and noticing the fact that the administration of anterior pituitary-like substances in most cases results in overgrowth of the external genitalia and premature puberty, gave such substances to a small group of children suffering from nocturnal enuresis. The ages of the children ranged from 5 to 9 years. In none of the children was there any frank anatomic defect. A commercial preparation of anterior-pituitary-like substance containing 500 international rat units per cc. was used. Injections were given two or three times weekly. In all of the cases appreciable improvement of the condition was noted within the second week of treatment and complete relief was observed in all cases before the end of the fourth week. The result of the treatment was prompt and spectacular and in no case were visible anatomic changes noted. Since the period of administration of the gonadotropic substance was of such short duration, no external signs of premature puberty were anticipated and none occurred. According to this author's concept, incontinence is not a physi-

ologic condition occurring at a certain age and its abolition does not come about through the establishment of precocious maturity of certain structures, but rather through the further development or maturation of these structures at a stage corresponding to the child's age.

Male sex hormones in the form of testosterone propionate were used by Bodechtal (8) and by Zehn (9) in the treatment of incontinence in adult males suffering from prostatic disorders and females who were nearing the menopause. These authors report striking favorable results and attributed them mainly to improved tonus of the bladder muscle produced by the use of this preparation. Zehn also used this preparation in the treatment of a number of children afflicted with nocturnal and diurnal enuresis. Daily injections in dosages up to 5 mg. were given for a short period, followed by injections given at intervals of 2 or 3 days. No other form of treatment was given to any of the cases. The results were excellent, in practically no case was there a failure, and in some the therapeutic result was quite spectacular.

#### CLINICAL PROCEDURE

Fifty children with enuresis were treated with male sex hormone preparations. Forty-six wet nightly or several times a night and 3 had both nocturnal and diurnal enuresis. None showed any sign of mental retardation. Of the 50 cases, 36 were boys and 14 girls. They were divided into two age groups; those 3.5 to 7 years and those 7 to 14 years of age. The first group comprised 17 boys and 7 girls. The second, 19 boys and 7 girls.

Methyl testosterone was given once daily, or twice in refractive cases, a dosage of from 10 to 20 mg. daily, which was continued for several weeks and then reduced or given less frequently after definite improvement or cure of the case. The intramuscular injections of the propionate ester of testosterone in oil was given once daily in a dosage of 10 or 25 mg. Testosterone in the form of a topical application was applied twice daily on the lower part of the abdomen, using about 8 mg. each day. After improvement or cure of the patient, the preparation was applied once daily and continued for about two months. Ten boys and 4 girls were treated in

this way. In 26 boys and 9 girls the male hormone was given orally and in one girl who had not responded to inunction or oral treatment, the preparation was given by intramuscular injection. In few cases was treatment continued beyond two months.

No other form of treatment except a restriction of fluid and a high salt intake was used. No other drugs were given. Except for some correction of gross environmental defects, no form of psychiatric treatment of the case was attempted. Careful dietary management along with fluid intake restriction was practiced in every case, and the child was awakened and made to pass urine in the early part of the night.

### RESULTS

The therapeutic results in the total of 36 boys showed 20 entirely cured, 11 improved and 5 unchanged in condition. Of the 14 girls 7 were entirely cured, 6 improved and one showed no change. The boys seemed to respond to the treatment more quickly than did the girls. In 13 of the completely cured cases the results with the treatment were prompt, occurring in less than 2 weeks.

In a few of the cases occasional wetting re-occurred when the treatment was stopped but immediately ceased when treatment with testosterone propionate was resumed. Very few of the completely cured or markedly improved cases required treatment beyond two months. One case required treatment for one year before the enuresis stopped entirely.

### DISCUSSION

In those children which showed no improvement there were, in practically every case, factors which no doubt contributed to the poor result. The mothers often admitted that they did not give the preparation regularly, or often, in the case of the older child they left the entire management of the treatment, such as fluid intake restriction and high salt intake and the medication to the child itself. These were, without exception the cases which responded poorly or showed no improvement at all.

It may be questioned whether the fluid intake restriction, the high salt intake and get-

ting the child up in the early part of the night might not in itself have been a major contributing factor in the cure or improvement and that the hormone treatment was really not the principal effective agent. That this was not the case is apparent since nearly all of the patients reported had been more or less and for long periods of time on this type of management, including the use of belladonna preparations, and had shown no improvement. The relapse of some of the cases when hormone treatment was stopped, and the prompt relief or improvement in the enuresis when treatment was resumed is further proof that the principal effect was probably due to the drug.

### SUMMARY

The net result of treatment with male sex hormone in the 50 cases of enuresis in children shows 54 per cent completely cured, 34 per cent much improved and in 16 per cent there was no improvement or complete failure. This percentage could no doubt have been improved had there been better and more careful control and management of the case.

The effect in some cases was quite dramatic and far more rapid than can be achieved with more general forms of treatment or the purely psychiatric approach to the problem. We are quite convinced that the use of male sex hormone preparations in moderate dosage, even if given over long periods of time in this age group, produces no lasting undesirable effects such as sexual precocity or unusual permanent enlargement of the sex organs.

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The testosterone for topical application, the methyl testosterone for oral use (Oreton M) and the testosterone propionate in oil for intramuscular injection (Oreton) were supplied by the Schering Corp. Bloomfield, N. J.



# Hyperparathyroidism: A Report and an Analysis of 13 Cases Occurring in the Middle Western States

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IT IS generally believed that there is a specific geographical distribution for hyperparathyroidism and that the disease is extremely rare in the middle western part of the United States. Wilder and Howell (1) suggested that vitamin D, the deficiency of which has been considered as an etiologic factor, was probably one of the causes for the disease being so extremely rare in this part of the country. The occurrence of 13 proven cases at the Uni-

pected, and to discuss some of the diagnostic difficulties.

## Analysis of Cases

The ages of the 13 patients varied from 20 to 60 years. Twelve were white and one was a negro. The sexes were about equally represented. Of these patients, 11 lived in Iowa, 1 in Ohio, and 1 in Illinois. They all had lived in the middle west for 20 years or longer. The

TABLE 1. INITIAL SYMPTOMS AND DURATION OF HYPERPARATHYROIDISM IN 13 CASES IN THE MIDDLE WESTERN STATES

Case	Weakness	Gastrointestinal	Presence of Pains and Aches of Muscles and Joints	Pain in Back	Pathologic Fracture	Bone Cyst	Genitourinary Symptoms	Duration, yr.
1								5
2			none		occurred			1/3
3				present	occurred			7
4	present				occurred	present		4
5	present	present					present	6
6	present	present						13
7	present	present		present			present	5
8						present		1/3
9			none				present	12
10			none			present		4
11				present				5/12
12			none	present				1
13	present			present	occurred	present	present	3

versity Hospitals in Iowa City during the past 12 years casts some doubt regarding the rarity of this disease in the middlewestern states. It appears pertinent, therefore, to call attention to the occurrence of these cases, to analyze their manifestations, ascertain which of the manifestations led to the disease being sus-

birthplaces were as follows: 7, Iowa; 1, Sweden; 1, Nebraska; 1, Oklahoma; 1, Pennsylvania; 1, New York; and 1, Russia. The occupations were as follows: 7, housewives; 1, clerk; 1, machinist; 1, blacksmith; 1, farmer; 1, teacher, and 1 had no occupation. The symptoms began from 4 months to 13 years before admission and the initial symptoms are shown in table 1. It will be noted that pains and aches in the

TABLE 2. SUBJECTIVE MANIFESTATIONS IN 13 CASES OF HYPERPARATHYROIDISM AT TIME OF HOSPITAL ADMISSION

	Muscle and Joint Aches and Pains	Weight Loss	Mass in Neck	Decrease Stature	Pathologic Fracture	Local Swelling	Genito-Urinary Symptoms	Gastro-Intestinal Symptoms	Cardiac Respiratory Symptoms
Present	12	8	4	7	4	7	7	8	6
Absent	1	2	9	4	9	6	6	5	7
Questionable	0	3	0	2	0	0	0	0	0

muscles and joints were the most common initial symptoms, in fact they were the pre-dominating symptoms in 7 of the cases. These pains are aching and boring in character, but frequently the patient is unable to describe them. They are usually located in the lower extremities and lower back, but in 3 of our cases they were present also in the shoulders and arms. There are no local objective manifestations, as a rule, but in 2 cases there was enlargement of the knee and elbow joints, respectively, and 1 patient had a history of generalized migratory swelling of the joints of the upper and lower extremities shortly before admission.

Pathological fracture was one of the initial symptoms in 4 cases. In 3 of these vague muscular aches and pains had been noted for indefinite periods previous to the fracture, but they were not of sufficient intensity to demand attention. In one case, however, the pathological fracture was the only symptom that was present.

Localized swelling surrounding a bone cyst was the initial abnormality noted in 3 cases. Of these, 2 had noted muscular and joint aches and pains previously and the appearance of localized swelling of the cyst caused them to seek aid. In one case, however, the deformity of the cyst was the only symptom experienced by the patient.

Genito-urinary symptoms such as dysuria, urgency and frequency were among the initial subjective manifestations in 3 instances. In 2 of these cases the genito-urinary symptoms

were the outstanding initial ones, but later they were over-shadowed by the muscular and joint pains. Symptoms had been present in 8 of the cases for 4 years or longer.

The subjective manifestations present at admission are shown in table 2. It is to be noted that muscular and joint aches and pains were the most constant, being present in 12 of the 13 cases. Gastroenteric symptoms and loss of weight occurred in over one-half of the cases. Symptoms referable to the cardio-respiratory and genito-urinary systems, decrease in stature and localized swelling due to bone cysts were present in about one-half of the cases.

The objective manifestations are shown in table 3. It will be noted that there were renal stones in 8 instances and bone cysts in 7 cases. The cysts were present in the mandible only in 2 cases and the teeth were abnormal in 5. The serum calcium was elevated in 10 cases and the phosphorus was diminished in 11. The serum proteins were decreased, however, in 4 cases.

Analysis of the records to ascertain which of the manifestations led to the suspicion of the disease is of interest. In 7 instances muscular aches and joint pains led to further investigation of the patient. In 4 of these the possibility of hyperparathyroidism was not apparently suspected until after roentgenograms revealed bony changes consistent with the disease. In 3 others, however, the disease was suspected before the roentgenograms were made. The data are shown in table 4. Pathological fractures led to further study in 3 cases, calcium deposits in the fingers in 1 case, cyst of the jaw

TABLE 3. OBJECTIVE MANIFESTATIONS OF HYPERPARATHYROIDISM IN 13 CASES

	Renal Stones	Cysts Jaw	Other Bone Cysts (by X ray)	Abnormal Teeth	Elevated Serum Ca	Decreased Serum P	Low Serum Protein	Elevated Serum Phosphatase
Absent	4	9	6	7	3	2	3	5
Present	8	4	7	6	10	11	4	6
Questionable	1	0	0	0	0	0	0	0

in 1, and dysuria in 1 case. Confirmation of the diagnosis in these cases is shown in table 5. It is to be noted that abnormal parathyroid glands were discovered in 12 cases at operation and in 1 at postmortem examination. Of these,

ful cases the elevated phosphatase and an increased urinary calcium were of value. Five cases were of particular interest. Case 3, a woman, aged 28 years, was observed on several occasions between 1934 and 1941 because of

TABLE 4. SUBJECTIVE SYMPTOMS LEADING TO SUSPICION OF HYPERPARATHYROIDISM OR TO FURTHER CASE STUDY AND OBJECTIVE MANIFESTATIONS IN EACH OF THESE

Case	Subjective Symptoms	Objective Manifestations		
		Roentgenograms	Serum Ca	Serum Phosphorus
1	Muscular and joint aches and pains	Bone cysts	Elevated	Decreased
2	Muscular and joint aches and pains	Osteoporosis and cysts	Elevated	Decreased
3	Path. fracture	Osteoporosis and cysts	Normal	Normal
4	Path. fracture	Osteoporosis and cysts	Elevated	Decreased
5	Calcium deposits in fingers	Osteoporosis	Elevated	Elevated
6	Muscle and joint aches and pains	Bone cysts	Elevated	Decreased
7	Muscular and joint aches and pains	Osteoporosis and cysts	Elevated	Decreased
8	Swelling of jaw	Osteoporosis and cysts	Elevated	Decreased
9	Dysuria	Renal stones	Normal	Decreased
10	Muscle and joint aches and pains	Bone cysts	Elevated	Normal
11	Muscle and joint aches and pains	Normal	Elevated	Decreased
12	Muscle-joint aches and pains and swelling of jaw	Bone cysts	Normal	Normal
13	Muscle pains; path. fract.	Bone cyst	Elevated	Decreased

11 were adenoma and 2 were hyperplastic glands. The latter cases are of interest. Case 3 showed very slight improvement 3½ months after operation and in the other case the gland was found at autopsy. One patient, case 13, died 2 days after operation in apparent cardiac failure. The other 10 patients showed definite improvement.

The diagnosis was not difficult to establish in most cases once it was suspected. The elevated serum calcium and diminished phosphorus were of aid in most instances. In doubt-

TABLE 5. PATHOLOGIC REPORT AND RESULT OF OPERATION IN 12 CASES OF HYPERPARATHYROIDISM<sup>1</sup>

Case	Pathological Report	Result of Operation
1	Adenoma	Improved
2	Adenoma	Improved
3	Hyperplasia	Very slight improvement in 3½ months
4	Adenoma	Improved
6	Adenoma	Improved
7	Adenoma	Improved
8	Adenoma	Improved
9	Adenoma	Improved
10	Adenoma	Improved
11	Adenoma	Improved
12	Adenoma	Improved
13	Adenoma	Died

<sup>1</sup> Case 5 was not operated. Autopsy revealed hyperplasia of parathyroids.

pathological fractures and bony changes characteristic of hyperparathyroidism. The serum calcium, phosphorus and proteins, and the urinary calcium were consistently normal. The phosphatase was elevated on all occasions and the urinary phosphorus on 2 occasions. The parathyroid gland removed at operation was hyperplastic and the improvement of the patient was questionable. Case 6, a negro woman, aged 52 years, had symptoms for 10 years. During the first admission to the hospital the disease was not suspected. On the second admission 6 years later, however, the disease was suspected but the serum calcium and proteins were within normal limits; the phosphorus, however, was diminished. Two months later the serum calcium and phosphatase were elevated and phosphorus was decreased. At this admission she refused operation and returned 9 months later. The serum calcium was 13.2 mg., phosphorus, 1.9 mg. but the phosphatase was normal. Urinary calcium estimations during this admission were found to be increased. Case 12, a white woman, aged 60 years, was found to have a bone cyst and the serum calcium varied between 10.0 and 12.0 mg., phosphorus between 4.0 and 5.0 mg., and the urinary calcium and phosphorus were normal. The serum proteins were normal.

et an adenoma of the parathyroid was removed and she improved. Case 5, a white male, aged 30 years, had calcium deposits in the fingers and elevated serum phosphorus. This case was reported in detail by Curtis and Feller (1) and was due, undoubtedly, to hyperplasia of the parathyroid, secondary to longstanding extensive renal pathology. Case 9, a white male, aged 47 years, had only urinary symptoms; renal calculi were present. She had had known hypertension for 17 years. The serum calcium, phosphorus and proteins were normal and an adenoma of the parathyroid was removed. It is not known whether or not hyperplasia of the parathyroid gland was secondary to the renal pathology. Failure to find the offending gland during exploration of the neck does not exclude the diagnosis of hyperparathyroidism. One of our cases was explored three times by excellent surgeons before the gland was discovered and removed from the substernal space.

#### DISCUSSION

Inquiry among men from large medical centers in the middle west reveals that cases of hyperparathyroidism are extremely rare in their clinics. Some of these men were among the first to report cases of this disease. It certainly cannot be said that they are unaware of the manifestations of the disease and it is extremely unlikely that the disease is overlooked in patients observed by them. Why then are we observing more of these cases than other clinics in the midwest? The answer, of course, is not known. The years in which our cases were observed are of interest. One was diagnosed in 1929, 2 in 1935, 1 in 1937, 4 in 1938, 1 in 1939, 1 in 1940, and 3 in 1941. These figures show that 9 of our cases have been observed during the last 4 years. This would indicate that we were becoming more conscious of the disease or that the incidence of the disease was increasing.

The possibility that vitamin D deficiency was a factor in the etiology of these 13 cases appears somewhat remote. Of the 7 housewives, 4 lived in rural communities and of the remaining 6 patients, 4 had led active outdoor lives. Special studies for vitamin A deficiency were made in 13 cases. Of these, 3 showed no evidence of

vitamin deficiency and 1 was considered to be borderline. Albright's (3) argument against the disease being a vitamin D deficiency brings out that the disease is rare in the negro. It is of interest that one of our patients was a negress who was fairly dark.

The diagnosis of the disease is usually relatively easy once it is suspected. The association of the bone lesions is so widely appreciated that they need no comment. Most of our cases exhibited bone lesions which aroused suspicion of the disease. In one case, however, the symptomatology suggested the disease and the diagnosis was established and proven without there being evidence of bone lesions. Albright (3) states that "it is of interest that no proven case has been published from any other clinic other than the Mass. Gen. Hospital in which no bone disease was present and which was diagnosed during life." The association of renal calculi with hyperparathyroidism has also been emphasized. Of our cases, 8 exhibited renal stones, but in only one, Case 9, was the urinary symptoms of sufficient intensity to cause the patient to be admitted to the urology service of the hospital. This is of interest in view of the fact that Dr. Flocks of the Urology Department has been so intensely interested in renal stones and has been acutely aware of hyperparathyroidism as an etiologic factor in renal calculi.

The variation in the calcium and phosphorus metabolism in some of our cases observed over periods of months or years convinces us that the disease may have remissions and exacerbations. In such cases the gland apparently becomes overactive and then quiescent. The overactivity may never become very great, but this cycle continues over periods of years before the diagnosis is established. In such cases it may be very difficult to establish the diagnosis upon metabolic changes alone. An evaluation of the subjective and objective manifestations will aid in making the decision as to whether or not the parathyroid glands should be explored or the patient should be examined at frequent intervals in hopes of observing a period of overactivity of the gland.

As a rule the subjective and objective findings make the diagnosis without question. The bone pathology, increased serum calcium, de-

creased serum phosphorus, and elevated blood phosphatase establish the diagnosis fairly well, provided other destructive bone lesions are excluded. In cases with bone lesions without demonstrable alteration of calcium and phosphorus metabolism, exploration of the parathyroid glands may be necessary to establish the diagnosis. It should be borne in mind, however, that abnormal parathyroid tissue may be present and not discovered at operation; also, that the parathyroids may become hyperplastic secondarily to other disease and the discovery of this does not establish the diagnosis of primary hyperparathyroidism. In other cases evidences of bone pathology and renal calculi may be absent and the diagnosis is strongly suspected from the subjective manifestations and metabolic alterations.

#### SUMMARY

Thirteen cases of hyperparathyroidism are reported, all of whom lived in the middle western part of the United States. The manifestations present and those which caused the disease to be suspected and, in addition, the diagnostic difficulties are discussed.

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# Hexestrol: Clinical Study of a New Synthetic Estrogen

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THE DISCOVERY of the estrogenic properties of certain stilbene derivatives by Dodds and coworkers (1-3) in 1937, and the further demonstration of its estrogenic activity by others (4-5) led to the introduction of diethylstilbestrol into clinical use. To date a large number of clinical reports have demonstrated the therapeutic value of diethylstilbestrol, but the drug has the drawback that its administration is followed by nausea and vomiting in a variable percentage of cases.

Further search for the ideal synthetic estrogen that would not cause these toxic symptoms led to the study of a new compound isolated by Campbell and coworkers (6-7) which was identified by them chemically as 3,4-di-p-hydroxyphenyl-n-hexane and named hexestrol. These and other workers (8-11) have demonstrated the estrogenic properties of this new compound, hexestrol Bishop and coworkers (11), Freed (12), and Bieren and Compton (13) have reported clinical studies on hexestrol. There is much discrepancy in these three reports concerning the relative activity of hexestrol, as compared with diethylstilbestrol, which demonstrates the need for further controlled studies of this new estrogen to determine its biological activity and to study its toxicity.

This report is concerned chiefly with the toxicity of the drug as shown by the amount of nausea and vomiting it produces, and by laboratory tests. Previous investigators have found that hexestrol is less toxic and less potent than diethylstilbestrol (13).

Permission to do this research was granted by the Research Committee of the Jefferson Davis Hospital, Houston, Texas

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Hexestrol was furnished for this study in tablets of 0.2, 1 and 3 mg., in a solution in corn oil containing 1 mg per cc. and in crystalline form, from which a solution in olive oil containing 25 mg. per cc. was prepared.

TABLE 1 INCIDENCE OF NAUSEA AND VOMITING WITH HEXESTROL BY MOUTH

Daily Dose	Patients Treated	Patient Exhibiting Nausea	Patients Exhibiting Vomiting
mg	no	no	no
1	18	0	0
2	22	0	0
3	12	0	0
6	15	0	0
9	18	4	0
12	26	5	0
18	19	5	0
24	21	6	1
Total	152	20	1

TABLE 2 INCIDENCE OF NAUSEA AND VOMITING WITH HEXESTROL PARENTERALLY

Injection 2-3/wk	Patients Treated	Patients Exhibiting Nausea	Patients Exhibiting Vomiting
no	no	no	mg
50	20	4	1
75	23	16	6
100	19	14	12
125	12	11	11
200	13	13	12
250	10	10	10
300	8	8	8
500	5	5	5
1000	6	6	6
Total	116	87	71

It is apparent, from tables 1 and 2, that hexestrol produces nausea and vomiting less often than diethylstilbestrol. The total incidence of nausea following oral administration was 13 per cent. Patients could tolerate 50 mg.

of hexestrol intramuscularly without nausea, but when 75 to 100 mg. was given, approximately all (95%) of the patients had nausea, and when 125 mg. was given, all of the patients developed nausea within 4 to 6 hours. Fifty per cent vomited from 1 to 5 times the first day. On the second, third and fourth days there was nausea only; there was no nausea subsequently.

In contrast, 87 per cent of the 3223 patients receiving diethylstilbestrol experienced nausea after 5 mg. orally or after an injection of 5 mg. of the drug (14-16). From this data it can be concluded that if diethylstilbestrol and hexestrol are given in similar dosages, diethylstilbestrol causes an incidence of nausea over 6 times that of hexestrol.

To compare hexestrol with diethylstilbestrol, in regard to the production of uterine bleeding, 26 menopausal and 28 normally menstruating patients were given 3, 6 and 12 mg. of hexestrol orally 2, 3 or 4 times a day.

The reason for giving hexestrol in the above dosages was to learn if it was possible to produce uterine bleeding similar to that produced by 1 mg. of diethylstilbestrol daily for a period of 20 to 46 days (17). Regardless of the amount of hexestrol given none of the menopausal patients bled. This is an advantage over diethylstilbestrol since 52 menopausal patients had bled after taking diethylstilbestrol in 1 mg. doses daily for 20 to 46 days, even though they had not had a menstrual period for 1 to 28 years. In the earlier studies some of the patients who continued taking the 1 mg. doses of diethylstilbestrol after bleeding started, flooded so badly that they had to be hospitalized and have a dilatation and curettage in order to stop the bleeding (17). Later it was found that this bleeding could be more easily and conveniently controlled by giving from 10 to 25 mg. of diethylstilbestrol by mouth every 15 minutes until the bleeding stopped, which was within 4 to 6 hours (17).

*Nausea.* The percentage of 152 cases experiencing nausea as the result of 3 to 6 mg. of hexestrol daily was 12 per cent, while that resulting from 3 to 6 mg. of diethylstilbestrol daily was 87 per cent (18). The nausea from hexestrol in these doses was very mild and was not followed by vomiting in any instance. Therefore, it is our impression, from this study,

that hexestrol is preferable to diethylstilbestrol for the treatment of menopausal symptoms.

It has been observed, as reported by Biere and Compton (13), that some patients who were not relieved of menopausal symptoms with diethylstilbestrol were relieved when given hexestrol, and vice versa. There were also a few menopausal patients who were not relieved of menopausal symptoms by either of these synthetic estrogens, but who were relieved by taking natural estrogens. Patients who had received both diethylstilbestrol and hexestrol for menopausal symptoms preferred the latter because it did not produce nausea.

*Normal menstrual cycle.* Twenty-eight patients in whom menstruation was diagnosed as normal by means of a premenstrual biopsy were given 3, 6, 9 and 12 mg. of hexestrol orally 3 times a day for 96 days. Endometrial biopsies were made premenstrually during the treatment and every second month after hexestrol in every instance the biopsy tissue revealed normal premenstrual endometrium. From this it is apparent that hexestrol is much less potent as an estrogen than diethylstilbestrol, since 3 women with normal menstrual periods who took 0.5 mg. of diethylstilbestrol daily did not menstruate regularly and the endometrium was never premenstrual in character (17, 18).

The patients were required to keep accurate charts of the menstrual cycles every month. The 28 patients who received 18 to 27 mg. of hexestrol per day, reported that the menstrual flow was as regular as usual but that the amount of flow was less. Hexestrol given in these doses produced hypomenorrhea.

*Dysfunctional uterine bleeding.* Since the above observation indicates that hexestrol might be used in the treatment of dysfunctional uterine bleeding, 18 such cases were treated with hexestrol as follows: a) In cases in which bleeding had already stopped, 6 mg. was given 3 times a day for 6 months along with tolerated doses of thyroid. Accurate menstrual records showed in each case that bleeding recurred cyclically and was normal in amount and duration. b) If the patients were bleeding profusely, 100 to 250 mg. of hexestrol was given into the anterior wall of the cervix, or intramuscularly, using a spinal needle and a 10 cc. syringe. Following this, 3 to 6 mg. of hexestrol was given 3 times a

may. Bleeding usually stopped in from 2 to 8 hours after the large dose of the drug. All of the patients were nauseated and 82 per cent vomited at least once within 5 to 12 hours after the large dose of hexestrol was given. In all of the 18 cases menstruation became normal lasting from 1 to 3 days less than the usual time. The patients estimated that the amount of flow was reduced 25 to 50 per cent.

*Dysmenorrhea.* In 6 cases of dysmenorrhea 1 to 6 mg. of hexestrol was given 2 to 3 times a day. Five of the 6 reported that the flow was less in amount and duration and were relieved of dysmenorrhea. The sixth patient had more pain than usual at menstruation.

*Senile vaginitis.* Eight women having senile vaginitis were given 3 to 6 mg. of hexestrol, 2 to 3 times a day. The thin atrophic vaginal mucosa came to resemble that of the normal vagina. Two of the 8 patients became nauseated and stopped the drug. The pH of the vagina, as determined by a Beckman pH instrument, was 7.23 before the hexestrol was given and after 5 to 6 days the pH was 4.8 to 5.2. When hexestrol or diethylstilbestrol is given (0.5 mg. or more per day over a period of 20 days or longer), a marked hyperplasia of the cervical glands is produced with the result that cervical secretion with a pH of 7.6 to 8.0, passes out of the cervix and a false reading of the vaginal acidity will result if this possibility is not taken into consideration.

*Gonococcal vulvovaginitis.* Three patients with a gonococcal vulvovaginitis were given 1 to 3 mg. of hexestrol by mouth daily for 14 to 28 days. The vaginal smears became negative within 7 to 9 days. A fourth case has been hospitalized for 32 days and takes 3 mg. of hexestrol daily. The smears continue to be positive for gram-negative intracellular diplococci.

#### Laboratory Studies for Toxicity

The toxicity of hexestrol has been studied by doing routinely, before the beginning of therapy and every 2 to 6 weeks thereafter, complete blood counts, urine analysis, blood cholesterol, blood Ca, uric acid, blood sugar, NPN, electrocardiograph and blood Cl determinations, and roentgenograms of the sella turcica. No abnormal changes in the blood were found that would indicate toxicity. In one series

of 143 women there were 597 blood studies made.

Thirty-two patients who were scheduled for some type of gynecological operation were studied and were given, prior to operation, a total of from 14,000 to 15,000 mg. of hexestrol in from 1 to 214 days as shown in table 3.

TABLE 3. DOSAGES OF HEXESTROL USED IN TOXICITY STUDY

Case	Total Dosage	Days of Treatment
	mg.	
1	2,692	102
2	3,368	47
3	3,479	92
4	648	28
5	2,343	102
6	4,455	180
7	2,878	44
8	300	3
9	500	3
10	315	1
11	1,211	82
12	1,542	43
13	776	126
14	800	101
15	2,565	103
16	612	88
17	2,188	110
18	1,230	185
19	1,602	140
20	2,064	157
21	15,000	214
22	5,630	86
23	4,125	92
24	1,980	92
25	1,002	49
26	109	54
27	4,250	89
28	1,167	102
29	111	112
30	315	93
31	250	1
32	14	14

This study made it possible to determine at the time of operation the effect of these amounts of hexestrol upon the female generative organs and to examine in many of the patients sections of the myometrium, cervix, vagina, endometrium, tubes and ovaries. There was no evidence of malignant changes and no abnormal pathology produced. The menstrual history was carefully recorded on these patients before, during and after the administration of the hexestrol.

In this group of 32 patients there were no abnormalities in the laboratory tests or in roentgenograms of the sella turcica before, during and after giving hexestrol. This would seem to indicate that hexestrol is a relatively non-toxic drug.

Fifteen patients were made amenorrheic for



periods ranging from 2 to 6 months by taking from 50 to 500 mg. of hexestrol daily. Their respective normal menstrual cycles were resumed after hexestrol was discontinued, and have remained normal for 6 to 18 months.

Patients who were nauseated by hexestrol did not develop a tolerance for it upon continued administration as is the case with diethylstilbestrol (18). Pregnant women were more sensitive to hexestrol than to diethylstilbestrol since 100 mg. of hexestrol given 3 times a week over a period of 2 to 16 weeks will more often nauseate the pregnant patient than the non-pregnant woman receiving the same dosage for the same period of time. As a rule, both pregnant and non-pregnant patients will become tolerant to diethylstilbestrol within 4 to 5 days (14, 15, 16, 19-24). There are exceptions to this, of course.

#### SUMMARY

Hexestrol which is a relatively weak estrogenic drug has been found useful in therapy of the menopause, dysfunctional uterine bleeding, juvenile vulvovaginitis and senile vaginitis.

In cases of menopause hexestrol was more effective than diethylstilbestrol because there was less nausea and no uterine bleeding as with diethylstilbestrol.

Doses of 3 mg. 1 to 3 times a day, were effective for the treatment of dysfunctional uterine bleeding and menorrhagia. The 3-mg. tablets were given at 9 P.M. for 3 nights, then one 3-mg. tablet 3 times a day for 3 days. The 3-mg. dose was gradually increased every day until tolerance was reached, which was usually 3 to 6 mg., three times a day. The medication could be taken only at night if the patient wished. If the bleeding was severe, 75 to 100 mg. of hexestrol was injected at once into the anterior wall of the cervix or intramuscularly, followed by 6 to 9 mg. orally every 15 minutes until bleeding stopped, then 6 to 9 mg. 3 times a day for 3 to 4 months along with 1 to 5 grains of thyroid per day for 6 to 12 months. In the case of nausea, nembutal,  $1\frac{1}{2}$  grains or phenobarbital was given.

In menopause cases, the patient was given 0.5 mg. of hexestrol orally 3 times a day for 2 days, then the dosage was increased by 0.5 mg. every 2 days until the patient determined the amount required to relieve the menopausal symptoms.

Due to the fact that we were unable to produce uterine bleeding with hexestrol, as occurs with diethylstilbestrol, and that we could control 89 per cent of the menopause cases with hexestrol, we believe hexestrol should be used instead of diethylstilbestrol for the treatment of menopause symptoms.

Laboratory tests before, during and after the administration of hexestrol were normal, so it is apparent the drug is not very toxic even in large unphysiological and experimental doses.

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# Estrogen Pellet Therapy in the Menopause

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IN THE TREATMENT of patients with menopausal symptoms, estrogen replacement therapy has earned for itself a well-established place. The procedure of administering the hormone parenterally two or three times a week, in order to maintain a sufficient level in the tissues, has decided disadvantages; it is time-consuming for both the patient and the physician, and the frequent hypodermic injections are disagreeable. In order to circumvent the inconvenience and unpleasantness of administration, the use of the orally active estrogen, stilbestrol, has become widespread among gynecologists and practitioners.

There can be no doubt of the effectiveness of stilbestrol in controlling menopausal symptoms, but its administration is often associated with undesirable side effects. We have found that 12.5 per cent of 32 patients in the dispensary, and a much higher percentage among private patients, who were treated with oral stilbestrol, were required to discontinue it because of nausea and vomiting. It has been demonstrated that many patients can take very small doses of stilbestrol without nausea or vomiting, but the percentage of relief of symptoms in a dosage of 0.5 mg. or less is much smaller than when the dosage is increased to 1.0 mg. daily. When this dosage, 1.0 mg. daily, is used, nausea and vomiting often necessitate discontinuance of the therapy.

Uterine bleeding is another side effect which is frequently noted when stilbestrol is given orally. When stilbestrol was administered in daily dosage of 0.5 mg. or less, there was uterine bleeding in 8.8 per cent of the cases; of the group which had received a dosage

of 1 mg. or more per day, 36.3 per cent bled abnormally. Since a dosage of 1 mg. or more is frequently necessary for relief of symptoms, it is obvious that bleeding in over a third of the cases is a decided disadvantage. In a small group of 7 cases we attempted pellet implantation with stilbestrol. Five of the 7 women bled abnormally, an incidence too great to make implantation with stilbestrol a practical method of treatment. It is noteworthy, however, that all of these 7 women were relieved of their menopausal symptoms. The bleeding is usually not profuse but occurring, as it does, during years when malignancy must always be seriously considered, a curettage is necessary to rule out cancer. The disadvantage of bleeding, of course, does not apply to those cases of the surgical menopause in which there is no uterus; it is in this group that we believe stilbestrol to be most useful.

Because we have not been entirely satisfied with either the parenteral use of the natural estrogens or with the oral use of stilbestrol, we have sought another method of administering the hormone. In 1937, Deanesly and Parkes (1) announced a new technique in hormone administration in animals whereby solid pellets of crystalline hormone were implanted subcutaneously, to be absorbed slowly and continuously over a long period of time. Such pellets were found effective in producing prolonged hormonal stimulation in laboratory animals. In 1938, Bishop (2) implanted a pellet of estrone subcutaneously in a young castrated woman who reported partial relief of menopausal symptoms; this relief lasted for 5 weeks. In 1940, Bennett, Biskind and Mark (3) reported their results on 21 menopausal women treated with subcutaneous pellets of theelin

(estrone). They found that relief of subjective symptoms began on an average of 2 weeks after the implantation and persisted for as long as 14.5 weeks. They also discovered *a*) that the urinary estrogen level rose and remained elevated for correspondingly long periods, *b*) that the urinary level of gonadotropic hormone was depressed in 60 to 70 per cent of the cases

we have also reviewed the work done by Twombly and Millen (6) with 20 mg. pellet of estradiol implanted through a 10-gauge needle. In the same publication we cited the work of Mishell (7) who implanted large pellets of crystalline estrogens obtained by extracting pregnant mare's urine. One pellet was implanted in each instance through a small incision just above Poupart's ligament. Eighteen of 19 women so treated were relieved of their menopausal symptoms. We reported in a previous publication (4) our results in 45 women treated by implanting multiple small pellets of theelin (estrone), and described the technique which we employed. Since then we have had much larger experience based upon a total of 225 implantations in 133 patients and it is upon this experience that we wish to report. Because the technique of implantation is not generally known we will describe it here.

#### TECHNIQUE

The pellets are made by direct compression of crystalline estrone means of a punch and hammer in a steel plate, bored with small cylindrical openings 1.8 mm. in diameter. The solid steel plate is screwed tightly beneath this plate to hold the material in the small cylindrical compartment. After the pellets have been compressed the lower solid plate is removed and the pellets punched out. They are 1.83 mm. in diameter and

vary from 2 to 5 mm. in length and weigh from 5 to 10 mg. each. Such pellets could be made easily on a commercial basis, but they are not yet available. Labor and material shortage due to the war has prevented their manufacture. The pellets are sterilized in a dry steam autoclave at 250° F. under 15 pounds of pressure for 30 minutes. The implantations are made through a 12-gauge hollow needle fitted with a stilet (fig. 1). The pellets are loaded, with sterile forceps, into the pointed end of the needle, after the stilet has been withdrawn. The skin over the gluteal region is prepared

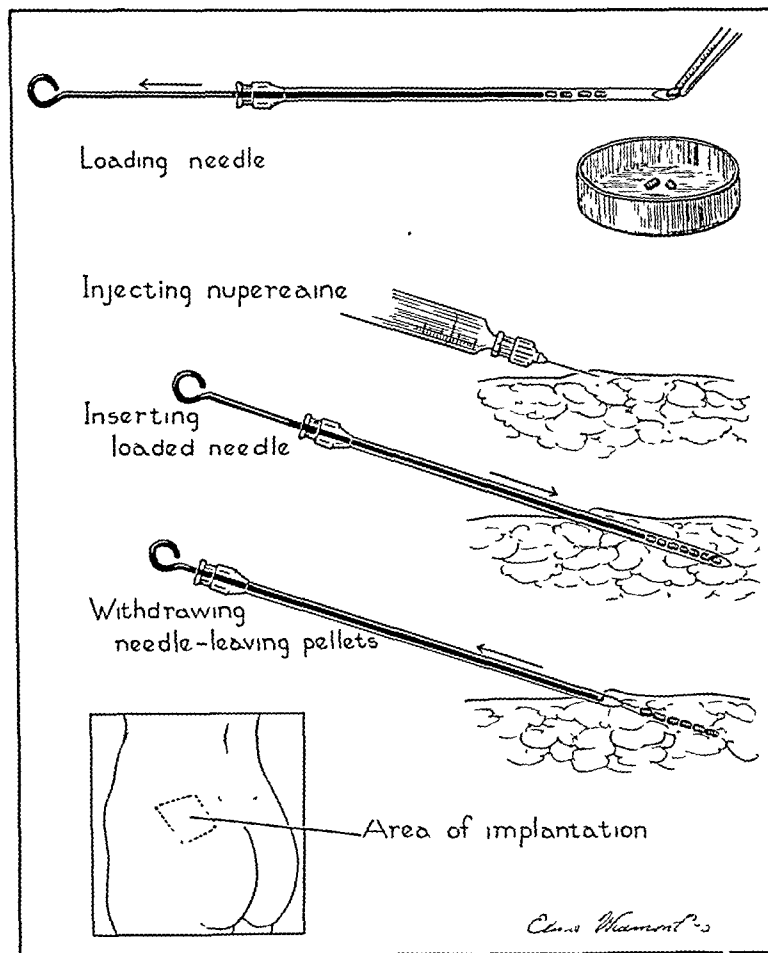


FIG. 1.

and *c*) that prolonged stimulation of the vaginal mucosa occurred as observed in biopsy specimens. These objective findings were interpreted as showing, beyond doubt, that the theelin was absorbed continuously from the pellets over long periods, and that the estrogenic action of the absorbed theelin was not impaired by the pellet method of administration.

In a previous publication (4) we have reviewed the work of MacBryde, Freedman, Loeffel and Allen (5) on the implantation of pellets of stilbestrol through small incisions and

by painting with full strength tincture of iodine which is allowed to dry and then washed off with alcohol. A spot is infiltrated with 1:500 procaine solution and the loaded needle inserted obliquely beneath the skin. As the needle is withdrawn the stilet is pressed in and the pellets are implanted subcutaneously. A small dry gauze dressing is placed over the injection site and left there for a week. The implantation is quite painless and can be done easily as an office procedure.

Because a foreign object is being introduced into the tissues, the most rigid sterile technique must be observed. In over 225 implantations we have had 3 relatively severe infections, and these occurred in the earlier days of our experimenting when the skin was prepared with alcohol alone. In none of these cases of infection did the implanted pellets slough out but there was a rather indurated, reddened area at the site of implantation. This necessitated the use of a protective dressing for a few weeks; in one instance, hot applications were used.

It is interesting to note that these cases complicated by local infection showed little or no relief of symptoms. This indicated, we believe, poor absorption due to fibrosis and to diminished blood supply about the infected foreign material. One of the patients, who had a local infection and who received no relief, had had a previous implantation with complete relief. A third implantation which was free from infection, resulted, again, in complete relief.

Because, then, of this danger of infection, the gluteal region is prepared for implantation by painting with full strength tincture of iodine and washing it off with alcohol. Since we have used this method of antisepsis we have had no infections and conclude that the danger of infection is negligible when proper technique is followed.

**Dosage** In our last 150 implantations we have standardized the dosage at 50 mg. This amount of hormone usually is contained in 6 to 7 pellets. Smaller dosage would shorten the period of effectiveness, and greater dosage, representing a larger quantity of foreign material, would enhance the foreign body re-

action about the pellets and, possibly, increase the danger of infection.

#### CLINICAL RESULTS

In evaluating results we have, as have most other investigators, considered the relief of hot flashes to be the most definite criterion of success. In our first publication (4) we reported satisfactory results in 93.4 per cent of the treated cases. In our present larger series of 133 patients in whom 225 implantations were made, the results have continued to be equally good. Approximately two weeks usually pass before sufficient estrone is absorbed to become effective. There are exceptions to this rule, however, for we have observed a complete cessation of menopausal symptoms within a week after the implantation. On the other hand, in a few individuals, a month has elapsed before the flashes have subsided. If no benefit is observed within a month there is usually no subsequent benefit. As a rule the flashes disappear gradually, there being a progressive diminution in intensity and frequency. With the subsidence of the flashes the feeling of nervous tension likewise disappears, and a feeling of well-being is established.

The relief of symptoms lasts, on an average, 4 months, but occasionally the flashes return after a shorter lapse of time; relief for 7 to 8 months is not uncommon. In a few instances, there has been no return of menopausal symptoms for an observed period of two years. We are inclined to regard these permanent 'cures' as cases in which the menopausal symptoms would have been of relatively short duration even without the implantations. We have seen no evidence that the normal period of adjustment of menopause is shortened by this substitutional therapy; nor have we been able to observe that it is lengthened. When the flashes do recur after a period of freedom, following an implantation, they usually recur in a milder form and are easily controlled by another implantation. Six is the maximum number of implantations which we have given to any one patient. These implantations have been given during the last 3 years, and at each implantation relief has been afforded.

It has become apparent to us that the best

results are seen in women who are treated relatively early after the onset of symptoms. The results are not as striking in those cases in which menopausal symptoms have been present for 3 or 4 years, the patient having become entrenched in her symptomatology. Also, one cannot be certain of the success of implantation treatment in obviously neurotic women; it is difficult, in dealing with them, to separate the real from the purely neurotic symptoms. However, we have used it, at times, as a therapeutic test in such individuals, and have frequently been surprised in the marked improvement in some of the patients whose symptoms we were inclined at first to regard as neurotic rather than menopausal.

With the exception of a few cases of infection at the site of implantation, which we have noted above, we have observed no untoward effects. Abnormal bleeding occurred only once in our first 28 cases previously reported, and we have seen it only a few times in the larger series of 133 cases. Since abnormal bleeding is common during the menopausal years one might expect coincidental bleeding occasionally. In fact, in a series of control patients which were treated with luminal, there was abnormal bleeding in 6.3 per cent, a greater incidence than occurred in our patients treated with estrone implantations.

#### CONCLUSIONS

From an experience of 3 years with the implantation of estrone (theelin) pellets we have concluded that it is the most satisfactory method yet proposed of treating the menopause. It has the advantage over the parenteral administration of the estrogenic hormone in oil in that one implantation results in a sustained absorption and prolonged relief of symptoms. It has the advantage over the oral administration of stilbestrol in that there are no untoward gastrointestinal symptoms, and there is no evidence that uterine bleeding is induced by it as is frequently the case with stilbestrol. The method is safe when proper methods of antisepsis are used, and it is sufficiently simple to carry out as an office procedure.

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# A Case of Myxedema with Macrocytic Anemia Successfully Treated with Thyroid and Testosterone

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THAT myxedema is usually associated with anemia is a well established clinical observation. It has also been observed that thyroidectomy in the experimental animal or in man is followed in the majority of cases by a moderate anemia. Stern and Altschule (1) reported that hyperchromic and macrocytic anemia of moderate severity complicated total thyroidectomy in a group with heart disease. The latter anemia resembles exactly the simple hyperchromic type described by Bomford (2), in his classification of the anemias in spontaneous myxedema, as the uncomplicated anemia of myxedema. He regards it as a result of a decrease in the size of the erythron which takes place in hypothyroidism as a physiologic compensation for diminished need of the tissues for oxygen, and to be akin to the anemia which appears in animals exposed to atmospheres of oxygen tension greater than normal. In other words, Bomford considers that thyroxine influences erythropoiesis only indirectly, insofar as the consumption of oxygen by all tissues is concerned, or as it may affect gastric secretion. He further observes that

this simple hyperchromic anemia is never severe, the color index is normal or a little above one. There is some macrocytosis but no poikilocytosis and no excessive anisocytosis. The reticulocyte count may be normal or a little above normal. The gastric function may be normal or there may be achlorhydria. The administration of liver or of iron has no effect on the anemia but the anemia does respond slowly to treatment with thyroid alone, in such doses as are found to keep the patient free from symptoms of myxedema or overdosage. The rate of response is very slow, the

blood count attaining normal levels in from three and a quarter to nine months.

In the light of more recent clinical and experimental observations it seems that this process of the regeneration of the blood may be enhanced or augmented by the addition of testosterone to therapy with thyroid extract. In the treatment of hypogonadal males in recent years it is not uncommon to note a striking increase in the blood count after the administration of testosterone. The hypochromic anemia of the eunuchoid responds readily to treatment with androgens. Experimental observations such as those of Steinglass (3) indicate that testosterone stimulates, whereas estrogen depresses, the function of the bone marrow.

McCullagh and Jones (4) also demonstrated that testosterone raised the blood count of hypogonadal males and that withdrawal of the hormone lowered both the hemoglobin and the count of the erythrocytes.

Because of the above observations the case being reported herewith was subjected to a trial of combined thyroid and testosterone therapy.

## CASE REPORT

On Aug. 8, 1938 a 71-year-old male, E. W. W., was admitted to the hospital with the diagnosis of a refractory pernicious anemia complicated by cardiac decompensation. He had been treated for many months prior to admission with liver extract and iron, without benefit. In the hospital the myxedema and cardiac failure were quite apparent, as was the anemia. The history indicated progressive intolerance of cold, weakness, somnolence, unsteady gait, pronounced bloating (especially unusual puffiness of the eyes), dry

skin with sparse lifeless hair on the scalp and body, thickness of the tongue, croaking voice and very dull mentality. The symptoms had been coming on for 3 to 5 years, the exact onset being uncertain.

Physical examination revealed a classical example of spontaneous myxedema (fig. 1, left). The skin was

the rhythm regular; the blood pressure was 160/110 mm. Hg. There was passive congestion of the liver and lungs; the presence of ascites was uncertain. All psychosomatic reactions were sluggish. The initial laboratory findings are depicted in table 1.

The initial electrocardiogram showed the character-



FIG. 1 (left). Patient E.W.W. when first hospitalized for treatment of myxedema heart and macrocytic anemia. August, 1938. (right) Patient after thyroid administration had relieved the cardiac decompensation. Note loss of myxedema. October, 1938.

edematous, of cafe-au-lait color; the voice hoarse and croaking; the tongue smooth and thick. There was no lymphadenopathy; the right submaxillary salivary gland was hard and about 3×2 cm. in size. The thyroid was slightly larger than normal. The heart was very much enlarged, its tones distant, the rate 62 and

istic depression of the T wave as well as a widened QRS complex (fig. 2, left), which is less constant in myxedema. The chest roentgenogram revealed marked enlargement of the heart and some pulmonary passive congestion (fig. 3, left).

TABLE 1. RESULTS OF MISCELLANEOUS DIAGNOSTIC TESTS ON ADMISSION, AUGUST 8, 1938

B.M.R., %	minus 50
Blood cholesterol, mg.	278
Icteric index, units	11
Total blood protein, gm.	7
Gastric analysis	Free HCl 65°
Venous pressure, cm. Hg	15
Venous pressure after r.u.q. pressure rise to 22.5 cm.	
Circulatory time: arm to lung, seconds	13
arm to tongue, seconds	31
Blood volume index	1.1
Sternal puncture, marrow	normoblastic
BLOOD COUNT	
Hb. (Sahli)	61%
r.b.c. 2,800,000/cu. mm.	Smear: macrocytes ++
c.i. 1.1	slight anisocytosis
w.b.c. 3,000/cu. mm.	occasional polychromatophilia
neutrophils 52.0%	occasional stippled cell
eosinophils 4.0%	platelets, normal number
lymphocytes 38.0%	
Reticulocytes	1.6%

It may be safe to assume that this cardiopathy was the result of myxedema, but a moderate hypertension may also have been contributory. In keeping with the diagnostic evaluation was the prompt and satisfactory response of the heart failure to bed rest and thyroid extract alone. Digitalis was not necessary. The shrinkage in the size of the heart as well as the progressive increase in the positive character of the T wave became apparent after thyroid therapy (fig. 2, right).

With continued thyroid feeding there was complete clearance of myxedema and a gradual return of a sense of well being. But there was no improvement in the anemia during the entire hospital regimen of almost 3 months. The blood count remained practically unchanged. One brisk reticulocytosis was followed by a fairly stable normal reticulocyte count. Figure 4 indicates the blood count in percentage of the normal, assuming 5,000,000 r.b.c./cu. mm. as normal, and the B.M.R., which returned to normal levels before discharge from the hospital. It is self evident that the

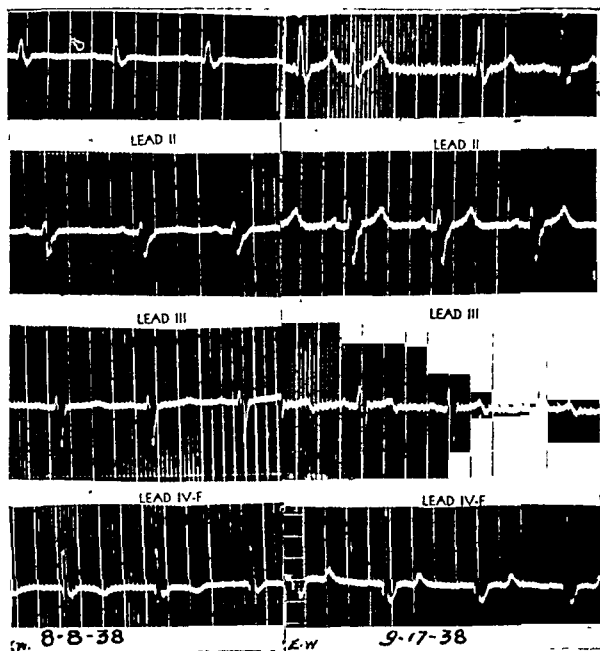


FIG. 2. Myxedema heart *a*) on admission showing the characteristic depression of the T wave and the less typical widening of the QRS complex; *b*) after 5 weeks of bed rest, showing positive T wave; widening QRS complex still present.

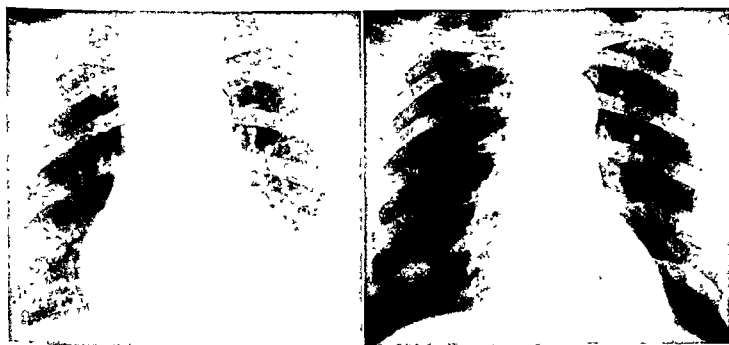


FIG. 3 (*left*). Myxedema heart with congestive failure Aug. 10, 1938 (*right*) Striking shrinkage in size of heart after bed rest and 2 grains of thyroid daily Sept 19, 1943.



cure of the myxedema was accompanied by a considerable loss of weight (fig. 1, right).

Liver extract and iron was tried for a short period but without any apparent effect on the blood count.

seemingly failed to influence erythropoiesis, testosterone propionate was injected intramuscularly 10-mg. doses twice weekly. Methyl testosterone substituted after 450 mg. of testosterone prop

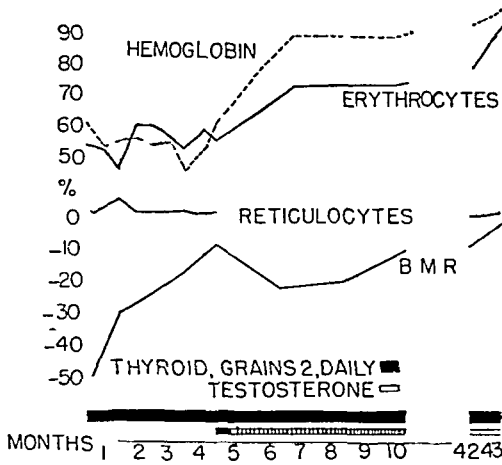


FIG. 4. Response of blood count in percentage of normal in a case of spontaneous myxedema, after treatment with thyroid and testosterone. The control period of 4 months during which treatment with iron, thyroid and liver extracts was followed by treatment with a) testosterone propionate, 450 mg. within a period of 2 years, and methyl testosterone, 1000 mg. within following 1 year; 200 mg. of the methyl testosterone was given within the first 10 days of the last month shown to induce a brisk rise in the blood count. A slight rise in the B M R but no change in the reticulocyte count was noted. A prompt erythropoietic response to testosterone is apparent at the beginning and end of the period of observation. The initial rise in blood count was sustained throughout. Note break in the curve to indicate lapse of 30 months during which there were no significant changes in any of the factors depicted.

It is noteworthy that thyroid extract given in dosage greater than 2 grains daily was apt to induce angina—hence this nominal dose has been maintained to date

had been given. To date about 1000 mg. of the testosterone has been administered orally along with the daily maintenance dose of 2 grains of the

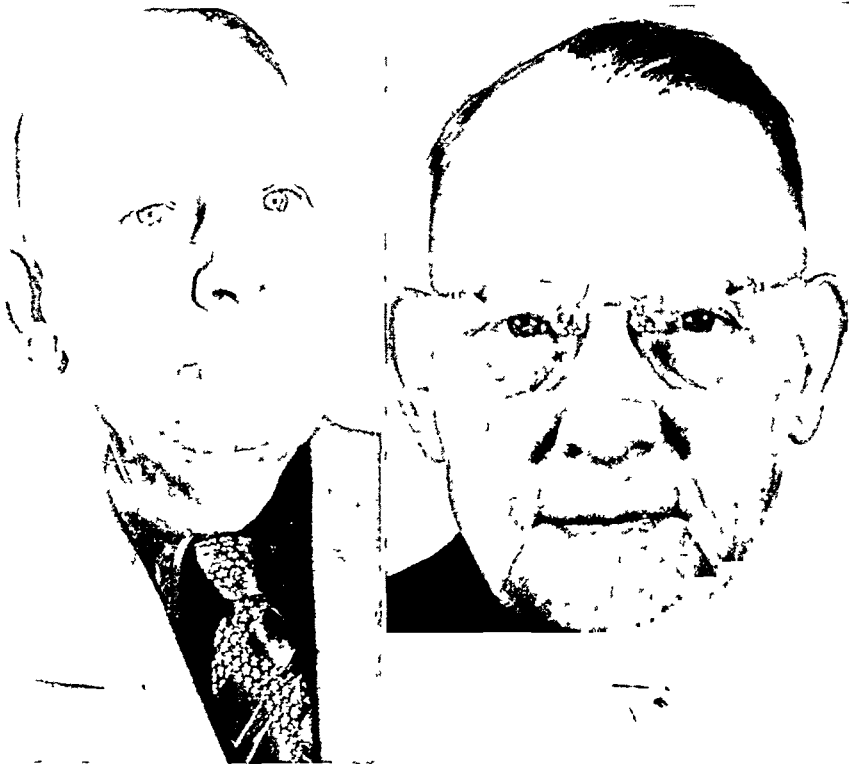


FIG. 5 (left) Patient E.W.W., December, 1941, aged 74 years (right). Patient in February, 1943, aged 75 years

(with occasional intermittance of one week's duration), with satisfactory symptomatic control.

In order to hasten the cure of the anemia it was deemed advisable to test the effect of testosterone. In January, 1939, after 4 months of thyroid feeding had

The dosage of testosterone has been kept mild (1500 mg. in 3 years) as a precautionary measure because, with the marked improvement in the patient's well being, it became increasingly difficult to restrain his physical activity. With a question-

myocardium in a senescent male it is better to err on the side of an insufficiency rather than too much testosterone

The response of the blood count to this combined therapy was prompt and very gratifying. It can be seen in figure 4 that even less than a physiologic dose of testosterone stimulated a prompt and substantial rise in the hemoglobin and the erythrocytes. This was maintained at slightly subnormal levels until a more physiologic dose of methyl testosterone (200 mg in

TABLE 2 BLOOD STUDIES, FEBRUARY 8, 1943

hemoglobin	91% (Sahl)	neutrophils	49	5%
hematocrit	4,790 000/cu mm	eosinophils	5	5%
erythrocytes	8 000/cu mm	basophils	1	5%
		lymphocytes	32	0%
		monocytes	11	5%
Smear, normal				
Hematocrit		44 Vol	%	
Reticulocytes		1 7	%	
Blood vol. index		0 88	%	
Color index		0 9	%	

days) was administered this year. This restored the blood count to normal. Note that the B M R and body weight were likewise stimulated to a more normal status by this increased dose of testosterone.

The character of the recent blood smear is in sharp contrast to that of those before treatment with thyroid. The macrocytes disappeared fairly early, the erythrocytes assuming normal shape, size and color during therapy (table 1 and 2). Figure 5 shows a gratifying transition of the patient from classical myxedema to normality.

## DISCUSSION

Recent clinical (4) and experimental work supports the concept that the endocrines influence erythropoiesis. This is particularly true of the thyroid and testicular hormones.

It might be speculated that inasmuch as the cause of the above discussed anemia was facilitated by the addition of testosterone to the usual thyroid therapy, any elderly or hypogonadal male with myxedema associated with anemia should profit by similar treatment. Here one may anticipate an augmentation of

the anemia by the hypogonadism. If this were true, then thyroid and testosterone would provide a more logical type of therapy than either one alone. Moreover, the patient is more promptly and completely rehabilitated with such combined therapy. To restore promptly a sense of normal well being by judicious combined organotherapy seems very worth while in such patients since time is of the essence in these situations.

In this connection one may further speculate on the value of combined thyroid and androgen treatment of certain refractory anemias, especially the so-called achrestic anemias, and those without apparent etiology other than senescence. The positive stimulation of the bone marrow by these hormones may provide a missing therapeutic link. Inasmuch as many of such anemias terminate fatally, judicious experimental trials with this organotherapy may be regarded as harmless.

## SUMMARY

An elderly male with a chronic untreated myxedema presented an associated hyperchromic macrocytic anemia. Four months of treatment with thyroid, liver extract and iron was without apparent influence on the anemia. When testosterone was added to the thyroid therapy the erythropoietic response was prompt and complete. It is suggested that similar anemias be given trials of such combined organotherapy.

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# EDITORIAL

## THE ENDOCINE PUZZLE OF HETEROSEXUAL HYPERTRICHOSIS (HIRSUTISM)

**A**N EMBARRASSING mustache and beard with excessive hair growth elsewhere on torso and extremities occurs far more frequently in adult girls and women than is generally supposed. It constitutes a distressing affliction, oftentimes a depressing torment and heartache for life.

Understandably, relief is sought at the hands of beauty specialists, before or after, or perhaps without ever consulting a physician. Often, sooner or later, in desperation, the patient is referred to an endocrinologist—for a miraculous 'gland-cure.' Hardly a month passes without the writer's being confronted with the unhappy duty of discouraging the victim's hopes and expectations.

For the majority of these unfortunates we have little to offer, either in explanation or therapy. Often the strange paradox has been uttered that it would be better for them if they were much worse—in that a cure might be possible if, in addition to superfluous hair of masculine distribution, there were also atrophy of the breasts, cessation of menses, and hypertrophy of the clitoris—pointing to an adrenal cortical tumor or an arrhenoblastoma of an ovary, removal of which could be counted upon to demasculinize and refeminize.

Extirpation of these androgenic-like tumors produces fairly prompt restoration of menstruation and gradual falling out of the abnormally-situated hair. The transformation would seem almost magical were it not convincing proof of the eradication of the underlying cause.

Unfortunately the overwhelming majority of hirsute women have no other complaints, and display no other abnormalities, than the heterosexual hypertrichosis. And in many of them it would appear to be simply an intensified familial racial characteristic, as in females of the Mediterranean peoples. A noticeable mustache at least is fairly common amongst them. It is more disconcerting and not readily explained when the hairiness exists in a female of English, Scotch or Scandinavian origin.

Not infrequently obesity accompanies the hirsutism. The fat may be confined to the upper half of the body ('buffalo' obesity, as in Cushing's

disease), or restricted chiefly to the hips, buttocks and abdomen ('girdle' type), or fairly generalized. Measures undertaken to reduce the adiposity fails to influence the hypertrichosis.

In other cases menstrual intervals may be prolonged and the flow reduced, but this additional factor offers little if any help in devising methods to counteract the hirsutism.

Since it became known that both sexes secrete both male and female sex hormones, it was tempting to assume that in hirsute women the normal ratio between these hormones had been altered in the direction of diminished estrogen and augmented androgen production. Consequently it would appear plausible to attempt counteracting the androgenic trichosis by administering estrogens (stilbestrol, estradiol). The results of such attempts have not been encouraging.

Recently Albright, *et al.*,<sup>1</sup> in an article entitled "A Syndrome characterized by primary ovarian insufficiency and decreased stature . . . with digression on hormonal control of axillary and pubic hair," suggests that, in females, this sexual hair is stimulated to grow by a hormone from the adrenal cortex. They claim further that pituitary dwarfs, whose adrenal cortices are atrophic secondarily, have no axillary or pubic hair whereas females suffering from primary ovarian insufficiency usually have moderate amounts and can be stimulated to grow axillary and pubic hair by estrin therapy. However seductive such an hypothesis may be, the writer thinks it pertinent to note that he has had a 19-year-old girl under intensive estrin therapy for several months; she had never menstruated, had absolutely no mammary development, and was totally devoid of sexual hair; she was of stocky build but her height was within the limits of normal (56 inches); most certainly she was not a pituitary dwarf. Estrin therapy has been successful in inducing vaginal bleedings and excellent mammary development, but not a single pubic or axillary hair has appeared during months of treatment.

<sup>1</sup> ALBRIGHT F., P. H. SMITH AND R. FRASER. *Am J Med Sc.* 204: 628. 1942.

It is not surprising that an adrenal cortical hyperplasia should be suspected as responsible for excessive hairiness in females (even in little girls), in view of the striking hirsutism and virilism, associated with adrenal cortical tumors and their cure by removal of the tumor. But bilateral partial adrenalectomy, for a supposed hyperplasia, is far too radical and hazardous a procedure for mere hypertrichosis, and inhibitory adrenal irradiation has not diminished the unpleasant hairiness.

In the absence of such an adrenal tumor or an arrhenoblastoma, endocrine therapy so far offers no solution for embarrassing beard and mustache, hair on the chest and thighs, and a masculine pubic escutcheon. Bleaching of the hair, in brunnettes, to render it less conspicuous, and skilful depilatory measures, are all that can be justifiably recommended. Electrolysis is an unending business and apt to be scarring if the beard is at all luxuriant.

H. L.



# LETTER TO THE EDITOR

## REVERSIBLE TESTOSTERONE-INDUCED VIRILISM

TO THE EDITOR:

The widespread use of testosterone propionate in the treatment of females with sexual and functional endocrine disorders has caused justifiable concern as to the dangers of induced masculinizing effects. Several reports in the literature have described virilism in the female as an unfortunate consequence of intensive androgenic therapy for gynecologic conditions such as dysmenorrhea, functional uterine bleeding and mastopathies. A case showing the transient nature of such masculinizing changes seems, therefore, worthy of mention since women who have become distressed over these changes may have some assurance that not in all cases are the change in voice, hairgrowth on the face, arms, legs and trunk, and enlargement of the clitoris, permanent disfigurements. Greenhill and Freed<sup>1</sup> have described the cases of two young women who received brief intensive courses of testosterone therapy and who developed alarming degrees of virilism.

Huffman<sup>2</sup> in a study of the effect of testosterone propionate upon reproduction in experimental animals (female rats) found that estrus was suppressed during androgen administration and that all female animals developed clitoral hypertrophy. He points out that the androgenic effect of the male sex hormone on the female animals is secondary to pituitary changes and that this effect is maintained only a short time after the injections are discontinued. All of his experimental animals had a return of normal estrus and bore healthy litters within 68 days after the treatment was terminated. Their progeny also bore normal offspring. Mazer and Mazer<sup>3</sup> have reported that of 38 women under androgenic therapy, 4 subsequently experienced normal pregnancies.

The reversibility of virilism induced by administration of male sex hormone appears to be an entirely reasonable possibility since even in the most prolonged and pronounced cases of adrenal cortical virilism the acne, hirsutism, amenorrhea, gruff voice, breast aplasia, hypertrophy of the clitoris and other changes undergo gradual correction after removal of the adenoma as was shown in the case reported by Lukens and Palmer<sup>4</sup> in 1940.

*Case report.* The patient is a married woman of 27, the mother of a normal boy age 5. Before androgenic treatment was given she had suffered from pulmonary tuberculosis and after thoracoplasty the disease was arrested. She had experienced severe migraine at increasingly short intervals since

the age of 15. The convalescence from tuberculosis was retarded because of the frequent bouts of nausea and vomiting brought on by the migraine and in consequence she was greatly underweight. Because of the general tonic and weight-increasing effects of male sex hormone she was given daily intramuscular doses of 25 mg. of testosterone propionate in sesame oil over a period of 17 days (Oct. 28 to Nov. 14, 1942) and then 9 doses over a period of the next 15 days (Nov. 14 to Dec. 2, 1942). In 35 days she therefore received a total of 650 mg. of testosterone propionate. After 3 weeks she had experienced an improvement in appetite and had gained 10 pounds in weight. A rather severe acne appeared on the chest and on the back. At the end of the treatment the patient complained of a marked growth of dark hair on her upper lip, cheeks and chin, on her upper and lower extremities and abdomen. Three weeks after termination of the treatment the growth of hair was more marked especially on the thighs and abdomen. Her voice had become husky, there was complete amenorrhea and the breasts had shrunk considerably. There was moderate enlargement of the clitoris. She was alarmed about these changes. There was relief from the migraine headaches but she had gained a total of 15 pounds in weight. The hirsutism remained stationary from Dec. 23, 1942 until about the middle of February, 1943 (approximately 9 weeks) when the patient noted an absence of hair on the abdomen, absence of acne, and a marked diminution of the hair on the thighs. By March first the excess hair on the upper lip, chin and cheeks had disappeared, the enlargement of the clitoris had disappeared, the breasts had been restored to their normal volume and consistency, and the voice had returned to normal pitch and timbre. The menstrual cycle was re-established in January of 1943, 45 days after termination of androgen therapy, and the subsequent periods have been more normal than in the two years preceding the treatment. On March 20, 1943, 109 days after the last dose of testosterone, a review of the situation showed that all of the induced changes had disappeared, except that about half of the weight gain was retained.

Male sex hormone has many valuable uses in the treatment of gynecological and functional endocrine disorders in the female. Medical men must be cognizant of the fact that with intensive treatment disturbing masculinizing effects may be the untoward concomitants of successful symptomatic relief. While justifiably alarming it is worth noting that in the instance described above, in which the changes toward virilism were substantial, they were, however, reversible in character. As has been stated by numerous investigators the gain in weight is due in part to the increased water retention but it is also attributable to the improved feeling of well-being and enhancement of appetite and general metabolism.

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<sup>1</sup> GREENHILL, J. P., AND S. C. FREED: *J. Am. Med. Assoc.* 113: 1573. 1939.

<sup>2</sup> HUFFMAN, J. W.: *Endocrinology* 29: 77. 1941.

<sup>3</sup> MAZER, C., AND M. MAZER: *Endocrinology* 24: 599. 1939.

<sup>4</sup> LUKENS, F. D. W., AND H. D. PALMER: *Endocrinology* 26: 941. 1940.

# CURRENT ENDOCRINE LITERATURE

Editor DANIEL A MCGINTY Collaborators ISRAEL BRAM, JOHN C DONALDSON, J W EVERETT, URRAY B GORDON, R B GREENBLATT, E C HAMBLIN, HANS O HATERIUS, CHARLES W HOOKER, R G HOSKINS, E HOWARD, J T LEWIS, T H MCGAVACK, A E MEYER, MARY L MILLER, C C PFEIFFER, DORIS PHELPS, P PRATT, E C REIFENSTEIN, JR, BORIS B RUBENSTEIN, PATRICIA H SMITH, RUTH ST JOHN, CHARLES W TURNER, EMERICH VON HAAM, HAROLD WOOSTER

## ADRENALS

ADLER, E H, AND S B ABRAMS

A case of Addison's disease associated with primary amenorrhea *Am J Obst & Gynec* 45 123 1943

The history, physical, laboratory, and X ray findings of a case of Addison's disease with associated amenorrhea in a woman aged 26 are presented. It was thought that the patient reached adolescence with normally developing pituitary and gonads. The disease probably began at this time. The absence of both estrogen and gonadotropin in the urine proved the presence of a pituitary deficiency. The failure of mature development of the gonads in this case was believed to be due to failure of the basophilic cells of the anterior lobe of the pituitary caused secondarily by their receiving inadequate stimulation from the adrenals. The patient's response was fairly good to the administration of 9 gm of sodium chloride daily, along with a high carbohydrate, high vitamin diet —E C H

HUIZENGA, L A, B L BROFMAN AND C J WIGGERS

Ineffectiveness of adreno cortical preparations in standardized hemorrhagic shock *Proc Soc Exp Biol & Med* 52 77 1943

Using a method of hemorrhagic shock which produced irreversible changes in about 85% of dogs, it was observed that of 17 untreated dogs, only 4 or 23.5% recovered on reinfusion of the withdrawn blood. Of 20 animals treated with adreno cortical preparations, 5 or 25% recovered, after the same experimental procedure. These observations fail to support the claims that cortical extracts exert a preventive or remedial influence in hemorrhagic shock —C W T

KEPL, M, G CALDWELL, AND A OCHSNER

Use of adrenal cortical hormone in *Cl welchii* infections in guinea pigs *Proc Soc Exp Biol & Med* 52 25 1943

When 13 guinea pigs weighing 9 to 12 oz were injected intramuscularly with 0.1 cc of a culture of *Cl welchii*, 12 died with an average survival time of 28.8 hr, with the classical picture of gas gangrene infection. Eleven animals were given 2 cc of adrenal cortical extract, each cc containing 25 dog units, one hour before infection and 6 injections of 2 cc every 4 hours thereafter. Of these, 6 died with an average survival time of 30 hours. Six animals were given 3 doses of 4 cc every 4 hours after infection. Five died with an average survival time of 47.5 hours.

When 0.2 cc of the culture was administered with cortical extract death was again delayed in comparison to the controls. These experiments indicate that adrenal cortical hormone extract has a protective value in delaying death in *Cl welchii* infections in guinea pigs —C W T

KOHLER, V, AND A FLECKENSTEIN

Treatment of ulcer with percortin *Deutsch Med Wochenschr* 68 476 1942

Relief from pain in gastric or duodenal ulcer is obtained in 2-3 days of daily intramuscular injections of 20-35 mg of desoxycorticosterone acetate. Case reports and roentgenograms illustrate the rapid healing. In all, 11 ulcer patients were improved by DOCA therapy after failure of bed rest, warmth, diet, and atropine. The asthenic, hypotonic, vasolabile constitution of ulcer patients is considered to be correlated with adrenal cortical insufficiency and the effects of DOCA are through its systemic action in this deficiency and also by direct action on the gastrointestinal mucous membrane. Benefit is also noted in gastritis —G A E

SARASON, E. L.

Adrenal cortex in systemic disease. A morphologic study. *Arch. Int. Med.* 71: 702. 1943.

The adrenal glands of 110 patients were studied in an effort to correlate cortical changes with systemic disease. Cortical enlargement associated with depletion of lipoid or reversal of lipoid pattern was found associated with inflammatory diseases, cachexia, pemphigus and protracted emesis. Cortical enlargement with an increased amount of lipoid was encountered in cases of hypertension; the change was more striking when the hypertension was associated with primary vascular disease. The explanation of these changes is not at hand. No significant alterations were present in the series of cases of atherosclerosis. Extreme enlargement was found in 4 cases of erythroblastosis fetalis. This study serves to emphasize that the enlargement of the adrenal cortex and the depletion of lipoid are reflections of the metabolic disturbances associated with certain systemic diseases and not the direct effect of the latter. *Author's summary.*—I.B.

WEICHERT, URSULA.

Treatment of the so-called Röntgen sickness with desoxycorticosterone. *Strahlentherapie* 71: 127. 1942.

Treatment of patients with desoxycorticosterone resulted in almost all cases in immediate improvement. Röntgen sickness, which resembles Addison's disease in many ways, is considered as due to adrenal insufficiency and results from increased protein destruction by irradiation.—D.A.M.

## ENDOCRINE GENERAL

ALLEN, E., AND L. B. DONALDSON.

The colostrum intradermal test for the diagnosis of pregnancy. *Am. J. Obst. & Gynec.* 45: 208. 1943.

The technic is described for the colostrum intradermal test for the diagnosis of pregnancy. Out of 164 known pregnant women, 13 cases with conflicting results were discarded. There were 151 cases considered in the calculation; of these the percentage of accuracy was 54.30. Of the non-pregnant cases, 87.65% was correctly diagnosed. The authors conclude that there was a difference either in potency in individual colostrum samples or a periodic change in individual sensitivity. Skin sensitivity apparently played a part in false

or incorrect reactions. They also believe that further work should be done on the hormonal content of colostrum.—E.C.H.

BENSON, R. E., AND J. A. BARGEN.

Chronic ulcerative colitis as a cause of retarded sexual and somatic development. *Gastroenterology* 1: 147. 1943.

Fourteen patients in whom chronic ulcerative colitis of the streptococcic type developed between the ages of 7 and 12 years exhibited severe retardation of growth and development. All presented a diminished linear growth with poor development of genitalia and absence of most of the normal secondary sex characteristics. Discussed in detail are the influence of nutrition, chronic sepsis and infection, hepatic disturbance and endocrine changes in the production of the condition. In 3 patients urinary assay for pituitary gonadotropins was attempted, but no hormone was found. This suggested to the author the possibility that in some instances of ulcerative colitis there may be secondarily an altered function of the pituitary gland.—T.H.McG.

BROWN, W. E., AND V. M. WILDER.

The response of the human uterus to epinephrine. *Am. J. Obst. & Gynec.* 45: 659. 1943.

The action of epinephrine was studied on three types of human uteri: (a) laboring uteri with spontaneous rhythm, (b) puerperal uteri exhibiting spontaneous rhythm, and (c) puerperal uteri with an oxytocically induced rhythm. The drug was usually given intravenously in the form of epinephrine solution 1:1000 in saline in one to two minim amounts. Observations were made by direct manometric methods. A premature contraction of the uterus was caused which was followed by a short latent period but without evidence of relaxation. Any apparent relaxation following epinephrine was always preceded by a period of increased activity. There was no difference in response in the spontaneously contracting uterus and the uterus with the oxytocically induced rhythm. There was no drop in tone indicating a relaxation. The use of epinephrine in disturbances of uterine contraction such as Bandl's ring, retraction rings, etc., is not recommended. It may be dangerous in these patients because of fatigue, dehydration and shock.—E.C.H.

CREEVY, C. D.

Hormones and carcinoma of the prostate. *Journal Lancet* 62: 452. 1943.

The author recommends that estrogen (stilbestrol orally, estradiol intramuscularly or as implanted pellets) be tried in every case of prostatic cancer not confined to the gland itself and at, if they fail, castration be performed.—*W.T.*

ARDNER, W. U., AND C. A. PFEIFFER.

Influence of estrogens and androgens on the skeletal system. *Physiol. Rev.* 23: 139. 1943.

Gonadal tissues and the steroid hormones elaborated therein exert influences on bone proliferation and possibly on the mechanism regulating calcium levels. In certain species sclerosis of cartilaginous matrix, proliferation and ossification of medullary osteogenic tissues are augmented by estrogens, serum calcium levels being, however, unchanged. Androgens tend to prevent excessive osseous growth in mammals treated with estrogens. It is assumed that stimulation of medullary proliferation by estrogen is due to direct effects on osteoblasts or on the differentiation of osteoblasts. Large amounts of estrogens inhibit growth of cartilage and bone and longitudinal osseous growth. Small amounts of androgen augment rate of longitudinal growth of the skeleton. The reviewers suggest that steroid hormones may find practical use in senile osteoporosis, healing of fractures or augmentation of osseous growth in certain hypogonadal patients. *D.A.M.*

LIST, S. H., AND SALMON, U. J.

Present status of endocrine diagnosis and therapy in gynecology. *Clinics* 1: 1197. 1943.

Endocrine therapy in the human female has undergone considerable change in the past few years. The literature dealing with the subject has assumed such vast proportions and appears frequently to be so contradictory that the practicing physician finds it difficult, if not impossible, to keep himself informed of all the new advances reported. The authors conclude to the effect that estrogen, pregnandiol and gonadotropic hormone determinations are appraised from the point of view of their practical value to the clinician as an aid in diagnosis. The value of morphologic diagnostic studies, namely vaginal smears and endometrial biopsies, is discussed. The present status of the endocrine treatment of the menopause and amenorrhea is reviewed. The value of androgens in the treatment of functional dysmenorrhea, pre-menstrual tension, functional menometrorrhagia and frigidity is briefly detailed.—*I.B.*

GOODFRIEND, J. R., AND M. DANIEL.

The histidine test (Kapeller-Adler) in the diagnosis of pregnancy. *Am. J. Obst. & Gynec.* 45: 140. 1943.

An accuracy of 91% was obtained with the histidine test on the urines of 56 pregnant women. There were five errors on the urines of 72 nonpregnant women of childbearing age, no errors on those of 26 climacteric patients, nor on 6 males. There was thus an accuracy of 95% in all the control groups together. The authors believe that the results are encouraging enough to warrant further investigation of the Kapeller-Adler test as a rapid method in the diagnosis of pregnancy.—*E.C.H.*

GREENBLATT, R. B.

Intracyclic bleeding. *Am. J. Obst. & Gynec.* 45: 299. 1943.

The ovulation syndrome of intracyclic bleeding or of midmenstrual pain was alleviated in six women, whose ages ranged from 19 to 39 years, by the use of chemically pure androgenic substance. The administration of testosterone propionate parenterally in 10 to 25 mg. doses at weekly intervals was effective, as was methyl testosterone orally in 5 to 10 mg. doses throughout the intermenstruum.—*E.C.H.*

GREENHILL, J. P.

Endocrine problems in gynecologic practice. *Med. Clin. North America* 27: 27. 1943.

This is a general outline of the subject, including physiologic considerations of pituitary and ovarian hormones, chorionic gonadotropin and the male sex hormone. Treatment of common gynecologic conditions as dysmenorrhea, amenorrhea, menorrhagia, premenstrual tension, the menopause and senile vaginitis receives practical comment. The author concludes with a note of caution against the indiscriminate use of hypodermic treatment in every endocrine disorder. The primary requisite is a correct diagnosis in which cancer must be ruled out in all cases of irregular bleeding. It is then that the proper endocrine product for the disturbance under consideration may be selected.—*I.B.*

HAMBLEEN, E. C.

Endocrine therapy in gynecology and obstetrics. *Am. J. Obst. & Gynec.* 45: 147. 1943.

A review article. The hormonal agents used in gynecology and obstetrics may be grouped thus:



(1) crystalline steroids which are hormones of the gonads and adrenal cortex or their derivatives and certain nonhormonal synthetic chemicals with endocrine-like properties; (2) extracts of protein or protein-like nature derived from the pituitary and thyroid glands and from certain body fluids.

The steroids are comprised of: estrogens, androgens, progestational principles and adrenal steroids. The 2 groups of estrogens are the hormonal and the nonhormonal steroids. The former are estradiol, estrone and estriol. The first two are usually administered intramuscularly in oil, and estriol is given orally. The best known of the nonhormonal estrogens is diethylstilbestrol, usually given by mouth. Estrogens have also been applied locally to the vaginal and nasal mucosae, by dermal inunction, and by subfascial implantation of sterile pellets. The indications for treatment with estrogens and the dosages in the following conditions are discussed: hypo-ovarianism originating in adolescence, anovulatory failure in adolescence, intercurrent ovarian failure during the preproductive epoch, the climacteric, pregnancy and the puerperium and other conditions not necessarily gynecologic in origin. The possibility of the carcinogenic rôle of estrogens should be remembered.

Up to the present time, no clinical studies have been reported which definitely associated any functional syndrome of the female with insufficient androgenic function; therefore, at present, androgenic therapy in the female is contraphysiologic.

Progestational principles, consisting of progestin, progesterone, and anhydro-hydroxy-progesterone, are discussed as to their efficacy in the therapy of abortion, dysmenorrhea, "afterpains" and prolonged or excessive functional uterine bleeding.

The indications for desoxycorticosterone acetate, the most widely used of the cortical steroids, are vomiting of pregnancy and preoperative preparation and postoperative care of patients requiring adrenal surgery.

The extracts of protein or protein-like nature are comprised of gonadotropins and thyroid substance. The gonadotropins may be divided into three groups, depending upon their sources: (1) pituitary, extracted from the pituitary gland itself; (2) chorionic, extracted from pregnancy urine; (3) equine, extracted from the serum of pregnant mares.

As yet, there are no extracts of the anterior pituitary which yield satisfactory clinical results.

In general, gonadotropic therapy has several limitations and undesirable qualities. However, equine gonadotropin may be used in adolescent estrogenic failure; and in patients with anovulatory failure, cyclic 1-2 gonadotropic therapy may be used. This embraces the administration of equine gonadotropin in daily doses of 400 i.u. for 10 days beginning on the fifth day of the cycle and beginning on the fifteenth day of the cycle. Chorionic gonadotropin is given intramuscularly in daily doses of 500 i.u. for ten days.

For therapy of relative corpus luteum failure the suggested dosage of chorionic gonadotropin is 500 i.u. daily for ten days beginning on the fifteenth day of the cycle.

The use of thyroid substance in function of uterine hemorrhage, in endocrine sterility and abortion is discussed.—E.C.H.

HAMBLÉN, E. C., D. V. HIRST AND W. K. CUTLER.

Effects of estrogenic therapy upon ovarian function. II. When employed during anovulatory cycles. *Am. J. Obst. & Gynec.* 45: 51 1943.

Sixteen patients were studied ranging in age from 15 to 35 years, who had presumed anovulatory ovarian failure predicated upon the occurrence of episodes of estrogenic bleeding. Endometrial biopsies were done prior to, during, and after therapy. The following treatment was given: estradiol was administered intramuscularly, and estriol glucuronide and diethylstilbestrol were given orally. Their administration was cyclic, i.e., from the fifth to the fourteenth day of the cycles of five patients, and from the fifth to the twenty-fourth days of the cycles of eleven patients. Daily dosages varied: those of estradiol benzoate from 0.33 to 0.67 mg.; those of estradiol dipropionate 2.5 mg. every other day; those of estriol glucuronide from 1800 to 4800 oral units; and those of diethylstilbestrol from 1 to 3 mg.

Twenty-two of the 26 biopsies studied during therapy continued to be of estrogenic nature. The four progestational responses in two patients were related to prolonged therapy with estriol glucuronide and were judged to be evidence of intercurrent recoveries of function.

It was concluded that the cyclic administration of moderate doses of hormonal and nonhormonal estrogens resulted in no direct stimulatory effects upon ovaries in anovulatory failure. Such therapy regulates the cyclicity and duration of flowing probably by direct alterations in the

functional capacities of the endometrial vessels. The ultimate salvage, which has been related to the cyclic combined therapy with estrogen and progesterone, seems to be dependent upon the two sequential use of and the synergism existing between estrogen and progesterone.—*E.C.H.*

HEIMAN, J.

Comparative effects of estrogen, testosterone and progesterone on benign mammary tumors of the rat. *Cancer Research* 3: 65. 1943.

Progesterone inhibits growth of the adenomatous portion of spontaneous rat mammary fibro-adenoma and reduces the percentage of takes of auto- and homotransplants. The tumor stimulating effect of 2.5 mg. estrogen is not inhibited by 18 mg. progesterone although smaller doses of estrogen are inhibited by 18 mg. progesterone. Progesterone alone does not affect bromas in castrated females and normal males but inhibits growth of the glandular portion of adenofibromas in castrated males. Combinations of progesterone and testosterone were somewhat more effective than progesterone alone in reducing percentage of takes in transplants and in inhibiting growth of the glandular fraction. Large doses of progesterone or testosterone were necessary to neutralize the stimulating effect of estrogen on growing fibro-adenoma. Rat fibroma, myxoma and sarcoma were not inhibited by progesterone. Progesterone does not inhibit growth of fibro-adenomas in pregnant rats, possibly because of high estrogen levels.—*D.I.M.*

HOFFMAN, MAX H.

Intersexual manifestations of nonendocrine origin. *Journal Lancet* 62: 446. 1943.

The case of a 16 year old boy with several abnormalities in his secondary sex characters including the lack of beard growth, the feminine type of pubic hair distribution and enlarged breasts is presented. Studies of the urinary sex hormone secretions showed low levels of both androgens and estrogens. The author suggests that the disturbed mechanism in the sex character development of this boy must be on a chromosomal basis rather than of endocrine origin.

A case of marked hirsutism of nonendocrine origin in a woman 48 years old was described. The beard and mustache was very heavy and dark. There was also a rather heavy growth of hair on the extremities and abdomen of the masculine type. Breast development was normal.

Postmortem examination showed that the right adrenal gland contained a greyish white tuberculous mass located in the medulla. The cortex was normal on macroscopic and microscopic examination. The pituitary, thyroid and ovaries were normal.—*C.W.T.*

JACOBY, A., AND B. RABBINER.

Clinical evaluation of testosterone propionate and methyl testosterone in dysmenorrhea and menometrorrhagia. *Am. J. Obst. & Gynec.* 45: 697. 1943.

Eighteen patients with dysmenorrhea and nine patients with menorrhagia and menometrorrhagia were treated with testosterone propionate and methyl testosterone. Complete relief of symptoms was experienced by four and improvement by eight of the dysmenorrhea patients and complete relief by six and improvement by two of the menometrorrhagia patients. In practically all cases there was a recurrence of the original ailment after discontinuation of treatment at varying intervals. Oral androgenic therapy, when given in adequate dosage, produced the same result as parenteral treatment.

It is believed that the basis of the alleviation of dysmenorrhea by male hormone in smaller doses could be the reduction of excessive contractions of the uterus. Again, the inhibition of the uterine contractility has been shown to decrease the volume of blood flow to the uterus, and thus the beneficial results on the menometrorrhagia. The recurrence of symptoms after cessation of therapy would seem to indicate that no permanent alteration in the patient's hormonal balance had been effected by the therapy of the duration described here.—*E.C.H.*

LUBIN, S., AND R. WALTMAN.

Missed abortion. An analysis of results following conservative management. *Am. J. Obst. & Gynec.* 45: 89. 1943.

A series of eighteen cases of missed abortion is presented where the dead ovum was retained for at least 28 days and up to 196 days. The ages of the patients ranged from 20 to 44 years. There were no alarming symptoms of retention, as toxemia, hemorrhage or infection. There was no maternal mortality and in only one case was there any morbidity. The Friedman test was found to be of value only when negative.

The change in one case in the pH of the vaginal secretions from acid to alkaline with the death of the fetus believed to indicate a fall in the estrogenic titer in the blood. It is thought by

some to be of greater value than the Aschheim-Zondek test in determining fetal death.

The hormonal method of induction may be attempted with estrogens first, to be followed later by pituitrin. Two of the authors' cases were given 1 mg. of stilbestrol daily for four or five days with good results. The only indication for surgical intervention was active bleeding.—*E.C.H.*

MCKELVEY, J. L.

Irregular shedding of the endometrium. *Journal Lancet* 62: 434. 1942.

The problem of irregular shedding of the endometrium in relation to an understanding of the menorrhagias is discussed. In a study of a small series of cases, it has been observed that estrogen and androgen excretion levels have been normal. Pregnan diol, however, continues to be excreted after the onset of menstruation. Thus irregular shedding is characterized by an abnormal prolongation of the excretion of pregnan diol.—*C.W.T.*

MILLEN, R. S., AND K. SHEPARD.

The association of vaginal bleeding to organic pathology and the endometrial pattern in the decades before the menopause. *Am. J. Obst. & Gynec.* 45: 812. 1943.

From a study of 3956 women with abnormal vaginal bleeding during the reproductive period, the suggestion is made that this complaint is not caused by any one organic pathologic condition or endometrial pattern, but rather it is a symptom often associated with pelvic disorders. These may be complications of pregnancy, cancer, benign tumors, erosions of the cervix and malpositions of the uterus. Each pelvic lesion is classified with its associated endometrial pattern. Abnormal bleeding may also occur in patients with grossly normal pelvic organs with the endometrial pattern of one of the normal cyclical phases, which are classified as follows: early follicular, follicular, early corpus luteum, and premenstrual. The atrophic, hyperplastic, hypertrophic, and mixed patterns, and those of adenomyosis and chronic endometritis are discussed briefly.—*E.C.H.*

REA, CHARLES E.

An evaluation of the clinical use of male sex hormone. *Journal Lancet* 62: 449. 1942.

A brief review of the physiological and pharmacological action of testosterone was given. The

chief indication for the use of male sex hormone is in the replacement therapy of the prepubertal and postpubertal castrates.—*C.W.T.*

REDDOCH, J. W., AND W. B. WIENER.

Stilbestrol in the termination of pregnancy. *Am. J. Obst. & Gynec.* 45: 343. 1943.

Twenty-eight patients, in whom for one reason or another, induction of labor seemed desirable, received stilbestrol with a total dosage of from 6 mg. to 720 mg. Beginning about 3 hours after the oil and enema, pitocin in small doses was given routinely except in patients in whom labor had started. The criterion for success was labor within 24 hours after the last dose of stilbestrol the day of the induction. Of the 28 cases there were five missed abortions, or abortions with five successes; 22 in whom an effort was made to aid in the induction by using stilbestrol with 9 successes, or 41%. There was one case of uterine inertia who was finally delivered with Dührsen's incisions.

There was no appreciable effect on lactation in any of the cases. As a part of the technique of medical induction, the use of stilbestrol was entirely justified in the author's hands.—*E.C.H.*

ROSS, R. A.

The involutional phase of the menstrual cycle (climacteric). *Am. J. Obst. & Gynec.* 45: 49. 1943.

Forty-one women during the climacteric or artificial menopause were studied. The fact was emphasized that this age should not be considered a disease, nor should it be considered as entirely dependent and definite with ovarian failures. The hormonology of the climacteric is discussed and may be summarized briefly: refractivity of the ovary to pituitary stimulation, failure of ovulation, gradual lag in the response to follicle stimulation with receding waves of estrogenic output, a temporarily uninhibited pituitary with varying adrenal and thyroid stimulation.

The complications of the climacteric are: irregular bleeding, vasomotor phenomena, abnormal normal psychic states, thyroid disorders, pelvic relaxation, and systemic breakdowns. These should be investigated before any therapy is attempted. This should consist of psychotherapy, correction of irregular bleeding, systemic treatment, necessary repair work, mild sedation and organotherapy. Estrogens are recommended in small doses by mouth. Diethylstilbestrol, if used,

should not exceed 1 mg. a day. Emmenin in doses of 480 to 960 day oral units may be given. (f) Androgen therapy is contraindicated.—*E.C.H.*

SAMUELS, LEO T.

Important advances in the physiology of the sex hormones. *Journal Lancet* 62: 419. 1942.

A brief review of recent literature concerning the following topics is given: The primary changes in tissues after estrogen stimulation. The general metabolic changes produced by the androgens. The rôle of the liver in the intermediary metabolism of steroid hormones. The extragenital origin of sex hormones. The large variety of compounds produced from the sex hormones during their intermediary metabolism. The rôle of the steroid hormones in the genesis of tumors.—*C.W.T.*

SCHWARTZ, R. M.

Pathology of postmenopausal bleeding. *Am. J. Obst. & Gynec.* 45: 522. 1943.

The pathology of 114 specimens from women past the menopause or over 50 years of age who had anomalous bleeding is reviewed. The percentage of benign lesions of the endometrium or cervix is 56.9, and the percentage of malignancy is 43.1. Endometrial hyperplasia represented 7.0% of the total. The cause for bleeding could not always be determined. It is stated that if menstruation and ovulation together end abruptly, the endometrium will be of the atrophic type. If the terminal cycles are anovulatory, the hyperplastic pattern may exist even in the absence of postmenopausal bleeding. After estrogenic production ceases, the pre-existing hyperplasia may show marked regressive changes in the epithelium and stroma.—*E.C.H.*

IEGLER, S. L., AND D. BAUER.

An evaluation of the pregnandiol complex as an index of ovarian and uterine function. *Am. J. Obst. & Gynec.* 45: 277. 1943.

Studies were done on the following women to evaluate pregnandiol excretion as a diagnostic index of ovarian and uterine function: 1. Controls; (a) 4 with normal menstrual cycles; (b) 2 with primary sterility; 2. Before and after hormone administration: (a) 6 with amenorrhea; (b) 4 with cyclic anovulatory menstruation; (c) 1 case of secondary sterility (2 previous abortions) and normal cycles; (d) 1 with bilateral salpingophorectomy, uterus intact; (e) 1 with supra-cervical hysterectomy, ovaries intact; (f) 1 with

complete vaginal hysterectomy, ovaries intact; (g) 1 with panhysterectomy. Sodium pregnandiol glucuronide was estimated according to the gravimetric method of Venning. Endometrial biopsies were done concurrently.

It was concluded that excretion of pregnandiol is not a positive index of ovulation nor of progesterone metabolism. It is often complementary to endometrial biopsy and basal body temperature studies, but it is impracticable for diagnosis in clinical practice because of its time-consuming nature and the fact that urinary specimens for 10 to 14 consecutive days must be examined to find a relative level of progesterone metabolism for one cycle.

The authors found that estrogens augment the metabolism and utilization of progesterone when the hormones are given simultaneously to an estrogen-primed uterus. Pregnanliol and endometrial biopsy studies did not show a consistency of administered gonadotropic hormones in establishing a biphasic ovarian response. The endometrium was found not to be necessary for the metabolism of endogenous and exogenous progesterone. It is suggested that some at present undefined hormone influences will prove to be important in the metabolism of progesterone and pregnandiol excretion.—*E.C.H.*

SMITH, O. W., G. V. S. SMITH AND S. SCHILLER.

Clinical experiments in relation to the excretion of the estrogens. III. Urinary estrogens in a normal menstrual cycle and in a case of essential dysmenorrhea. *Am. J. Obst. & Gynec.* 45: 15. 1943.

Urinary estrogens were done during one cycle on a 37 year old woman who had had a normal menstrual history since her menarche and had had two normal pregnancies. Results indicated that some luteal activity normally precedes ovulation and that estrogen degradation plays a physiologic rôle in the regulation of cyclic ovarian secretion.

Similar studies were done for three cycles on a 26 year old unmarried woman who had had fairly regular but consistently painful periods since her menarche. There had been no pelvic or organic abnormality to account for the pain in the five years that she had been under observation. Her urinary estrogens were very low, due to a comparative deficiency in luteal effect throughout the cycle. The shift in steroid metabolism at the start of the flow, pointing to a sudden increase in the rate of estrogen degradation, was less marked in this patient than in the normal.

It was thought that this might be significant in relation to the indicated subsequent comparative deficiency in normal growth and maturation of the ovarian follicle.

The above findings and the results of therapy with estrogens suggest an as etiologic factor in this case of dysmenorrhea the subnormal luteal activity with resulting incomplete premenstrual preparation.—*E.C.H.*

SMITH, O. W., G. V. S. SMITH AND A. G. GAULD.

Clinical experience in relation to the excretion of the estrogens. IV. The effect of veratrum viride upon urinary estrogens in pre-eclampsia. *Am J. Obst. & Gynec.* 45: 23. 1943.

Studies were done on a 23 year old woman with severe pre-eclampsia. Treatment with progesterone and estrogen and adrenal cortical extract showed that the administered hormones were being destroyed rather than utilized for the establishment of a more normal metabolism of the estrogens.

The administration of veratrum viride alone for four days markedly affected the excretion of estrogen metabolites by the temporary vasodilatation caused by this drug. The findings indicated a sudden decrease in degradation and increased metabolic conversion of the estrogens. The hormonal effects lasted no longer than the clinical.

It is believed that a reciprocal relationship exists between the vascular system and female sex hormones. An adequate vascular supply is just as important for the proper production and metabolism of the placental and ovarian steroids as adequate sex steroids are for genital vascularity. Thus, it would seem that any mechanical or organic disturbance which affects adversely the the blood supply to the placenta may be one of the primary causes for pre-eclampsia and eclampsia.

Therapy is suggested either as replacement therapy with estrogen and progesterone or by directly combating the vasoconstriction. The limitations of the former are apparent in this case. The principal drawbacks to the latter are the relatively short duration of the action of veratrum and its toxic side effects. The possibility of supplementing sex steroid therapy with veratrum viride should be investigated.—*E.C.H.*

SOULE, S. D.

A clinical trial of ethinyl estradiol. *Am. J. Obst. & Gynec.* 45: 315. 1943.

A series of 30 postoperative, postradiation a natural menopause patients were treated with ethinyl estradiol in daily doses of 0.05 mg. It was found to be therapeutically satisfactory and was tolerated in 93% of the cases. It is the most active oral estrogenic hormone used to date the author.—*E.C.H.*

SZEGO, C. M.

Methods of measurement of the naturally occurring sex hormones. *Journal Lancet* 62: 4. 1943.

A review of methods of measuring estrogen androgens, progesterone, pregnandiol and chorionic gonadotropin.—*C.W.T.*

TAYLOR, H. C., JR., F. E. MECKE AND G. TWOMBLY.

Estrogen and 17-ketosteroid excretion in patients with breast carcinoma. *Cancer Research* 3: 130. 1943.

Spontaneous excretion of estrogens and 17-ketosteroids was studied in numerous patients with or without various coexisting endocrine disorders. No abnormal values referable to breast cancer were found. When estrone, testosterone propionate and progesterone are injected in women, definite alterations occur in the rates of estrogen and 17-ketosteroid excretion in the urine and in the duration of the menstrual cycle. The exact alterations which occur depend to considerable extent on the time of the cycle at which the hormone is administered. Certain contrasts in the response to hormone injection were noted in a seven month study of one woman with breast cancer and one normal control. Differences in response reflect physiologic differences and suggest clinical methods whereby prediction of position to breast cancer may be sought.—*D.A.M.*

WERNER, S. C.

A quantitative study of the urinary excretion of hypophyseal gonadotropin, estrogen, and neutral 17-ketosteroids of normal men. *J. Clin. Invest.* 22: 395. 1943.

The subjects of these tests were 5 "healthy" men, two of whom, however, were undergoing a psychologic study at the time the analyses were made. Determinations were carried out in 1 patient for a month, and in all others for not less than 3 months. While the values for the 17-ketosteroids of the urine varied rather widely from patient to patient, for any single individual

they were reasonably constant from day to day and from week to week. Marked fluctuations are noted in urinary gonadotropins and estrogenic substances, which could not be related to each other, to 17-ketosteroid output, or to physiologic activity. No evidence whatsoever of any role in the excretions of these hormones was observed.—*T.H.McG.*

## GONADS

REY, L. B.

The nature and significance of the grooved nuclei of Brenner tumors and Walthard cell islands. *Am. J. Obst. & Gynec.* 45: 614. 1943.

The endocrine interest to this article lies in the author's statement that unpublished evidence of his indicates that the Brenner tumor is derived from the germinal epithelium of the ovary. The possibility of estrogenic output, therefore, should be investigated.—*E.C.H.*

ARRINGER, B. S.

Treatment of prostatic carcinoma. *Bull. New York Acad. Med.* 19: 417. 1943.

The author concludes that orchidectomy and stilbestrol treatment (5 mg. daily) should be the treatment in all cases of prostatic carcinoma. His therapy should be preceded by transurethral resection if urinary retention is a dominant factor. Transurethral resection is not necessary to establish diagnosis, aspirational biopsy being preferred. If the carcinoma is small and confined to the prostate and peri-prostatic region, radiation or total prostatectomy should be considered. Stilbestrol therapy is of definite benefit in controlling pain, causing some recession of prostate growth and improvement in general condition of the patient. It rarely has any effect on the metastases.—*D.A.M.*

AMPBELL, H. E.

Incidence of malignant growth of the undescended testicle. A critical and statistical study. *Arch. Surg.* 44: 353. 1942.

By critical analysis of available data, the author includes the undescended testicle is more susceptible to malignancy than is the scrotal and that the abdominal is more liable to malignant disease than the inguinal testis. The ratio of malignancy in the inguinal testis to that of the abdominal testis is 1 to 4. Analysis shows also that about 1 abdominal testis in 20 shows malignant change as compared to 1 in 80 inguinal.—*D.A.M.*

FERRIS, D. O.

Tumors of the testis: Correlation of pathologic characters with excretion of hormone in the urine. *Clinics* 1: 1026. 1943.

Tumors of the testis are rare, and almost all are malignant. Two types of tumor, seminoma and teratoma, comprise almost all malignant tumors of the testis. All malignant tumors of the testis cause excretion of excessive amounts of gonadotropic principle in the urine. Twenty R.U. per liter of urine is the dividing point between normal and excessive amounts. The test must be quantitative and the best technic is that of Frank. The best routine on the first analysis is to test for 25, 40 and 66 R.U. of hormone per liter of urine. Orchidectomy and subsequent extensive irradiation seem to be the best treatment. The survival rates compare quite favorably with results obtained in the treatment of malignant lesions elsewhere in the body. *Author's conclusions.*—*I.B.*

FOX, R. A.

Brenner tumor of the ovary. Case reports, discussion and bibliography. *Am. J. Path.* 18: 223. 1942.

Four instances of Brenner tumor are added to the 166 found in the literature. In 3 of the new cases and in 10 of those previously described, the tumors were bilateral and varied in size from tiny nodules to masses as large as a man's head. They were entirely solid or occurred as nodules in the wall of an ovarian cyst. They consisted mainly of fibrillary connective tissue with small nests of polyhedral cells. Central cyst-like spaces were lined with radially arranged columnar cells and contained mucoid secretion.—*D.A.M.*

GNASSI, A. M., J. B. FAISON AND M. FELLMAN.

Granulosa cell carcinoma. Report of 2 cases. *Am. J. Roentgenol.* 47: 458. 1942.

Two cases are reported in which rapidly fatal granulosa cell tumors with metastases occurred in women during the reproductive age. Treatment and surgery are discussed.—*D.A.M.*

GOLD, S.

Oestrogen therapy in testicular hypofunction. *Canad. M. A. J.* 48: 231. 1943.

Three patients with varying degrees of impotence due to testicular hypofunction were treated with male and female sex hormones and sodium

cacodylate. The author is inclined to believe that the improvement in potency 2 weeks after the injection of the sodium cacodylate was due to both the residual effect of the estrogenic hormone and the period of abstinence. Precordial pressure was frequently experienced by the patient during coitus while under treatment with the sex hormones, male and female. This precordial pressure was absent after the treatment with sodium cacodylate, an observation which justifies the suggestion that sex hormone therapy in elderly males may have a predisposition to cardiospasm following physical exertion, since neither the hormones alone nor the sexual exertion alone produced the pressure sensation over the precordium. The effect of the estrogenic hormones on the libido and potency was found to be quicker and more intense than that of testosterone propionate, in the stated doses.—*Biol. Absls.*

HAMBLEEN, E. C., D. V. HIRST, AND W. K. CUYLER.

Effects of estrogenic therapy upon ovarian function. I. When employed during normal menstrual cycles. *Am. J. Obst. & Gynec.* 45: 268. 1943.

Thirty healthy women with normal ovarian function were treated contraphysiologically with moderately small daily doses of hormonal estrogens: estrone 0.2 to 0.4 mg.; estradiol benzoate 0.33 mg. to 0.67 mg.; estradiol dipropionate 1.5 mg.; estriol glucuronide 450 oral units to 2400 oral units; and diethylstilbestrol 1 to 6 mg. Sixty-one cycles of therapy were administered during the first half of the ovarian cycle, i.e., from the fifth to the fourteenth day inclusive. Fifteen cycles of treatment extended from the fifth to the twenty-fourth day inclusive. Eight cycles of treatment were given during the last half of the cycle, i.e., from the fifteenth to the twenty-fourth day inclusive. Endometrial studies were made prior to, during, and after the cessation of the treatment. Sodium pregnandiol studies were done on nine patients before and during treatment.

It was found that estradiol dipropionate, when given intramuscularly in adequate amounts, depressed corpus luteum function. The other hormonal estrogens did not do so, presumably because of insufficient dosage. Diethylstilbestrol, even in moderately small oral doses, depressed corpus luteum function equally as much as did estradiol dipropionate. This was the only direct effect of estrogenic therapy on the ovarian level of function; it was not cumulative and did not

persist after therapy. The definite and quantitative alterations in the menstrual cycle were observed during therapy with estrogen given in larger doses probably resulted in action directly on the endometrium.—*E.C.H.*

JUROW, H. N.

Cyclic variations in the cervix of the guinea pig. *Am. J. Obst. & Gynec.* 45: 762. 1943.

Fifty-three normally cyclic virgin ferret guinea pigs were used for this study from on three months after maturity had been reached. Vaginal smears were taken during various stages of the cycle and stained with hematoxylin-eosin. Animals were sacrificed at various stages and histological studies made of the vagina, cervix, uterus and ovaries. It was found that definite cyclic change occurs in the cervix during the estrous cycle, which followed closely the variations present in the other parts of the genital tract, especially the vagina. These cyclic changes were felt to be dependent on the hormonal cycle.—*E.C.H.*

KUHN, C. L.

Ovarian autografts. *Am. J. Obst. & Gynec.* 45: 704, 1943.

This is a report of 38 cases of ovarian autografts done in an attempt to supply ovarian secretion to those patients in whom surgical removal of both ovaries was necessary because of some nonmalignant ovarian disease. Multiple (from 8 to 16) thin-sliced grafts from ovarian cortex into rectus muscle are recommended. These grafts functioned when transplanted into rectus muscle as shown by menstrual activity usually for years in all cases with an intact uterus, and by microscopic demonstration of corpora lutea in grafts excised one and two years after implantation. Patients with an intact uterus tended to have higher urinary estrogen levels.

Of the 26 patients who were followed 6 months showed relief from hot flushes and did not require estrogenic therapy. The choice between ovarian autografts and estrogenic therapy is a matter of judgment for the individual surgeon.—*E.C.H.*

MACK, H. C.

The glycogen index in the menopause. A study of certain estrogen functions based on a new method of staining vaginal smears. *Am. J. Obst. & Gynec.* 45: 402. 1943.

The iodine vapor method of staining vaginal smears is described as a rapid and simple means for the determination of the specific glycogen response to estrogenic activity in the human subject.

This method was used in studying 130 postmenopausal women ranging in age from 33 to 77 years to determine the incidence of glycogen overactivity, and the smears were graded according to glycogen content. The incidence of the 4 glycogen grades was calculated according to age, duration of the menopause, and the nature of the climacteric, whether spontaneous or artificially induced. The persistence of variable amounts of vaginal glycogen in these women gave additional evidence that estrogen was continuing to be elaborated by the ovary or extragenital sources.

It is suggested that there may be "antihorizontal" factors present in local and systemic ebrile states and vaginitis) which prevent the metabolic activity of estrogen and thus cause hypoenia.

The clinical usefulness of vaginal smear methods, including the one described here, is at present limited largely to the control of estrogen therapy in vaginitis and to investigations of potencies of commercial estrogens as judged by their effect on women with advanced glycopenic vaginal atrophy.—*E.C.H.*

NOVAK, J.

Testicular tubular adenoma in two sisters. *Am. J. Obst. & Gynec.* 45: 856. 1943.

Two cases of benign testicular tubular adenoma in two sisters are reported. Both patients looked and felt perfectly feminine, although the gonads consisted mainly of testicular tissue; the ovarian tissue was represented only by islands of ovarian stroma. Each sister had female external genitalia, a vagina, but no or almost no uterus and only a tiny tubal rudiment. Investigation showed that several other members of the family were affected with pronounced sexual abnormalities, the hereditary taint apparently having been transmitted from the grandmother to her children and grandchildren.

The gonads of these two cases were interpreted as ovotestes; the patients were intersexes. Embryologic facts and Goldschmidt's intersexuality theory are used to explain the origin of the malformation.—*E.C.H.*

LOTTINO, A., AND J. F. McGRATH.

Hyperplasia and luteinization of ovarian

stroma associated with masculinization. *Am. J. Obst. & Gynec.* 45: 863. 1943.

Two cases are reported of women, aged 36 and 38 years, respectively, with obesity, hirsutism and amenorrhea. One had hypertension. The removal of the ovaries produced no striking changes, although a primary complaint, headache, disappeared immediately in the hypertensive patient. The cause of the ovarian findings of stroma cell hyperplasia, theca cell proliferation and the clear cell islands is not known. The authors believe they do not represent a tumor but are a proliferative phenomenon induced by an endocrinologic imbalance affecting among other organs the ovarian stroma. Hyperplasia and luteinization of theca cells probably are manifestations of the same phenomenon modified somewhat by the proximity of these cells to the ovum.—*E.C.H.*

ROGERS, F. S.

Brenner tumor of the ovary complicating pregnancy. *Am. J. Obst. & Gynec.* 45: 896. 1943.

This is the fifth case of a Brenner tumor complicating pregnancy to be reported in the literature. It was removed without disturbance of the normal course of pregnancy.—*E.C.H.*

SIDDALL, R. S.

Sclerosis and related senile changes of the fallopian tubes. *Am. J. Obst. & Gynec.* 45: 785. 1943.

One hundred consecutive cases were studied which had had one or more definite fibroids in the uterus, at least one fallopian tube and one ovary removed and available for study, no salpingitis sufficient to distort the pathologic picture, no evidence of pregnancy and no irradiation treatment more than six weeks previously. It was found that with advancing sexual age, the fallopian tubes undergo certain changes consisting principally of a marked hypertrophy and sclerosis involving the connective tissue of the folds. Later, nonciliated and flatter cells replace the ciliated epithelium. This sclerosis, which was noted in 45% of cases with uterine leiomyofibromas, had little or no relationship to the size of the tumors. An investigation of another 100 cases corresponding to the above in every way except for the absence of fibroids, showed the condition in approximately the same proportion, the incidence increasing in both series with advancing age. Sclerosis of the fallopian tube was not related to previous pregnancies. Its incidence was



increased with the development of irregularities and anomalies of menstruation, and was most marked with the onset of the climacteric and afterwards. The same tendency was seen also with the histologic evidences (ovarian and endometrial) of sex hormone diminution. However, there were exceptions to the general rules.

Sclerosis was usually present in a small series of tubes associated with pregnancy, and therefore it is not an absolute barrier to pregnancy. However, it possibly might be a relative factor in sterility and also a cause of tubal pregnancy.

Doubt is cast upon statistical studies which apparently indicate a relationship between fibroids and certain other conditions, especially carcinoma of the uterine fundus.—*E.C.H.*

TAYLOR, H. C., JR., R. C. WARNER AND C. A. WELSH

The relationship of the estrogens and progesterone to the edema of normal and toxemic pregnancy. *Am. J. Obst. & Gynec.* 45:547. 1943.

Five patients are reported who received either estrogen or progesterone immediately after delivery in an effort to prevent or modify the sodium loss and diuresis of the early puerperium. In three of these patients large doses of hormones were also given during pregnancy to determine if the sodium balance was in any way disturbed by such treatment. Controls were five patients previously reported who were studied during late pregnancy and the early puerperium without hormone administration.

The sodium balance of the five hormone treated patients showed, with certain exceptions, the general trends observed in the cases previously reported. These consist in a constant retention of sodium until the time of delivery with a negative balance appearing after parturition and reaching its greatest magnitude from the third to the fifth day. The days of greatest sodium loss correspond in general with the return of the urinary estrogen to nonpregnant levels.

The absence of the postpartum sodium loss in one and its apparent reduction in another case of normal pregnancy after estrogen treatment in the puerperium seemed to show that one of the causes of sodium and water retention in normal pregnancy is the high estrogen concentration characteristic of the body fluids during that period. It was seen that progesterone may contribute to this by the fact that in the case which was treated with this, the loss of sodium substance in the early puerperium was relatively slight. The effect of estrogens and progesterone

on the prevention of diuresis and sodium loss in the puerperium of patients who had had toxemia of pregnancy was less convincing but still suggestive.

It was concluded that among several factors which cause edema in normal pregnancy most important is probably the physiological influence of the estrogens and progesterone on the excretion of sodium and water. Additional factors are no doubt at work in the edema of toxemia but it must be remembered that when the pregnant woman develops toxemia she is already physiologically conditioned to retain water readily. In this indirect sense at least the estrogens and progesterone may contribute greatly to the clinical manifestations and course of the disease.—*E.C.H.*

TOPKINS, P.

The histologic appearance of the endometrium during lactation amenorrhea and its relationship to ovarian function. *Am. J. Obst. & Gynec.* 45: 48. 1943.

A total of 145 endometrial biopsies was taken from 28 normal lactating women during the period of lactation amenorrhea. Of these, nine showed progestational changes, and all were associated with the onset of the first menstrual flow. One hundred and thirty-six specimens (94%) showed estrogenic changes, and of these twenty (15%) were hypoplastic.

It was concluded that the endometrium during lactation amenorrhea is not different from that found in amenorrhea caused by other factors; it shows diminished estrogenic stimulation. During lactation, the ovarian cycle is suppressed, ovulation does not occur. This is believed to be caused by suppression of the pituitary gonadotropic activity, due to prolactin or to some hormone of the lactating mammary gland.—*E.*

VEST, S. A., AND B. BARELARE, JR.

Androgens and the treatment of testicular hypofunction. *Clinics* 1: 1216. 1943.

The functions of the testicles, although not completely understood, fall into 2 general categories: the formation of spermatozoa in the seminiferous tubules for reproduction, and the secretion of hormones, presumably from the interstitial cells, responsible for certain body functions and physiological characteristics. The effects of the synthetic androgen testosterone depend much on its mode of administration, whether this be oral, by implantation, injection or topical application. The authors discuss the treatment

strates and eunuchoids, deficiency after puberty, and the response to testosterone proionate in various other conditions in which it appears indicated. The effects of androgens on growth, vascular system, impotence and psychiatric conditions, as well as on the "male climacteric," prostatic hypertrophy, male sterility, cryptorchidism and delayed adolescence are discussed. The authors warn against assigning undue therapeutic properties to testosterone proionate in certain far reaching clinical states.—B.

WILLIAMS, T. J.

Hydatidiform mole and associated tumors of the chorion. *Am. J. Ost. & Gynec.* 45: 432. 1943.

A discussion of hydatidiform moles and their subsequent course with a review of 24 cases is presented. They may be benign, their passage complete and recovery uneventful. In about half of the author's cases, chorionic tissue remained in the uterine cavity or in the uterine walls, and caused persistent positive biologic pregnancy tests. The presence of a persistent positive test following a mole, abortion, or pregnancy justifies the diagnosis of viable chorionic cells; however, too much reliance should not be placed on a single negative test because of the frequency with which the test becomes negative and then later positive. It is the custom of the author, in the presence of a persistent positive test, to perform curettage, and if a month or so later, the test is still positive, an abdominal exploration of the pelvis with hysterectomy is thought advisable. The cases recorded here have been classed microscopically as syncytial endometritis or syncytoma (infiltration with syncytium only), malignant mole or chorioadenoma (syncytium, Langhans' cells and villi), or chorionepithelioma (Langhans' cells and syncytium).—E.C.H.

WINTHER, N.

The endocrine factors in menstruation and its relation to dysmenorrhea. *Journal Lancet* 62: 428. 1943.

A study is reported concerning the effect of various hormones upon the estrogen and pregnandiol content of the urine of normal cyclic women. Gonadotropic hormone from PMS increased the output of estrogen but did not effect the excretion of pregnandiol. The administration of progesterone increased the output of pregnandiol but did not influence the output of estrogen. The administration of anhydro-hydroxy progester-

one, orally, did not increase the output of pregnandiol. There was no correlation between the estrogen and pregnandiol levels and the symptoms of dysmenorrhea.

A controlled clinical study indicated that the benefits from the use of estriol glycuronide in the treatment of dysmenorrhea were no greater than with placebo. A combination of estrogen and progesterone given concurrently may give better results.—C.W.T.

## HYPOPHYSIS

BARNETT, H. L., ANNE M. PERLEY AND P. HLINBECKER.

Influence of eosinophile cells of hypophysis on kidney function. *Proc. Soc. Exp. Biol. & Med.* 52: 114. 1943.

Two clinical cases are reported in support of the theory that the eosinophile cells of the anterior pituitary exercises a humoral influence on the kidney.—C.W.T.

GOLDZIEHER, M. A.

Diagnosis and treatment of pituitary disease. *Clinics* 1: 1069. 1943.

This is a rather comprehensive discussion of the subject in its various phases with 17 illustrative case histories. It is often more difficult to diagnose pituitary disease than most of the other endocrinopathies. The hypophysis is not only inaccessible to inspection or palpation in contrast to most other glands, but the symptomatology is also more varied and complex. Pituitary disease owes its protean character to the following 3 reasons: 1. The functional activities of the 2 lobes of the pituitary are multiple and may become dissociated in the course of disease, so much so that 1 or 2 of the varied activities are deficient while other functions remain unaltered. A combination of deficiency in one line with excessive activity in another is also noted. 2. The manifestations of disturbed pituitary function are produced often through the mediation of another endocrine gland, hence our attention is drawn to the secondary accomplice while the primary responsibility of the pituitary remains hidden. 3. Most of the essential metabolic processes are regulated directly or indirectly by the pituitary. Thus any disease of the gland is followed almost inevitably by metabolic disorders. However, the resulting symptoms may appear altogether unrelated to the primary glandular disease. The author classifies the various pituitary disorders

The maintenance of the blood sugar above certain critical levels is as essential to the living organism as is the continuation of respiration or the persistence of the heart rate. The endocrine glands form an important part of the sugar regulators of the body, which are directed mostly toward the avoidance of hypoglycemia. The author discusses the homeostatic mechanism of the liver, influence of the pancreas, the anterior pituitary, the adrenal cortex and the thyroid, the influence of liver dysfunction on blood sugar regulation, the clinical disturbances in the endocrine regulation of the blood sugar, and the intravenous dextrose tolerance test for liver dysfunction. A useful classification of the endocrine hyperglycemias and hypoglycemias is included.—*I.B.*

## PARATHYROID

COPE, O.

Hyperparathyroidism: The significance of general hyperplasia. *Clinics* 1: 1168. 1943.

The case described is the seventh in the author's series, in which the clinical picture was due to hyperplasia rather than tumor of the parathyroids. So rare are the cases due to parathyroid hyperplasia that doctors think of hyperparathyroidism as being always due to "a tumor." If this impression is not dispelled surgeons operating on a case with 4 hyperplastic glands will erroneously excise only 1 gland, with no benefit to the patient. The surgical problem in treating the patient with this pathology is more difficult since it involves doing a subtotal parathyroidectomy.—*I.B.*

ROSE, E.

Hypoparathyroidism. *Clinics* 1: 1179. 1943.

The principal causes of hypoparathyroidism are trauma and accidental removal of the parathyroids incident to thyroidectomy. In many instances acutely developed traumatic tetany is transitory and the symptoms may disappear spontaneously within a few days, weeks, or months, as the remaining parathyroid glands gradually regain their normal function or undergo compensatory hyperfunction. Often the damage is too severe to permit of spontaneous recovery. Untreated, various trophic and metabolic changes are apt to develop. These include lenticular cataract, perivascular cerebral calcification, dryness and brittleness of the hair and nails, dryness of the skin, muscular weakness, constipation, insomnia, psychasthenia, and gen-

eral slowing of the mental processes. Parathyroid tetany with convulsions may closely simulate epilepsy. Chronic latent hypoparathyroidism may produce a variety of vague misleading symptoms. Numbness and tingling, a feeling of stiffness and slight twitching of the muscles of the face or extremities may be important early signs. Acute hypoparathyroidism may follow the removal of a single hyperfunctioning adenomatous parathyroid gland and should be treated as an emergency. Intravenous injections of calcium gluconate or chloride and proper doses of parathyroid extract are the best therapeutic agents. Most patients eventually become refractory to parathyroid extract. Dihydrotachysterol or large doses of vitamin D are the agents of choice in the treatment of chronic hypoparathyroidism. In excessive dosage, both of these drugs can produce hypercalcemia. Continued maintenance of normal serum calcium levels is essential if the serious trophic and metabolic effects of chronic hypoparathyroidism are to be avoided or arrested.—*I.B.*

SOFFER, L. J., AND C. COHN.

Primary and secondary hyperparathyroidism. *Arch. Int. Med.* 71: 630. 1943.

The authors report 9 cases of hyperparathyroidism. In 5 of these cases the condition was primary, due to adenoma of a parathyroid gland and in 4 it was secondary, due to chronic renal disease, multiple myeloma and carcinomatous metastasis to the bones. The pathologic physiology, the clinical considerations and the treatment are discussed. The etiology of osteitis fibrosa cystica is usually an adenoma of a parathyroid gland. Occasionally there may be an adenoma of more than 1 parathyroid gland. However, primary hyperparathyroidism may result from hypertrophy of the parathyroids in the absence of actual tumor. The possible existence of a diseased aberrant parathyroid gland located in the mediastinum must be borne in mind.—*I.B.*

WOOD, T. R., AND WM. F. ROSS.

Does the parathyroid hormone influence phosphatase? *J. Am. Chem. Soc.* 64: 2759. 1942.

Parathyroid hormone solution accelerates the liberation of phosphate by kidney phosphatase. This is not attributed to any hormonal activity even in high concentration (75 u per cc. of digest) since other protein solutions or egg serum albumin exhibit the same property.—*D.A.M.*

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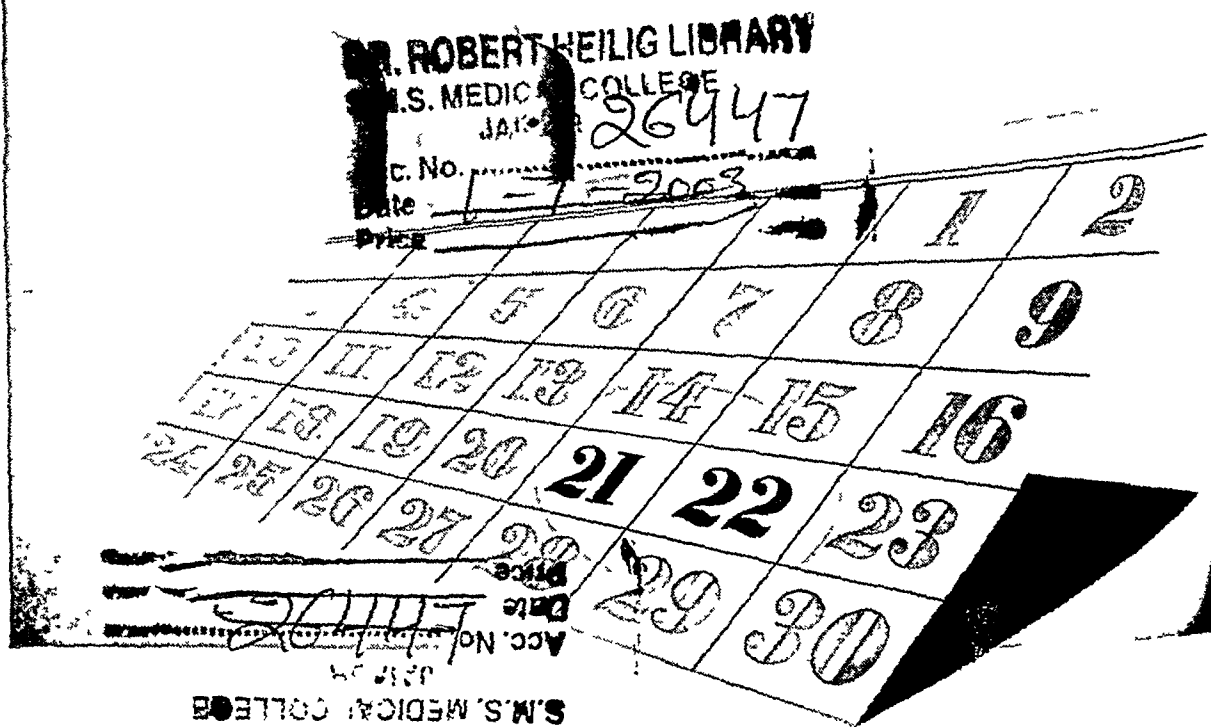
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\*B. Zondek, *J.A.M.A.*, 118 705, 1942;  
M. Berliand, *J. Clin. Endocrinol.*, 3457,  
1943; R. S. Finkler, *Am. J. Obst. &  
Gynec.*, 48 26, 1944.

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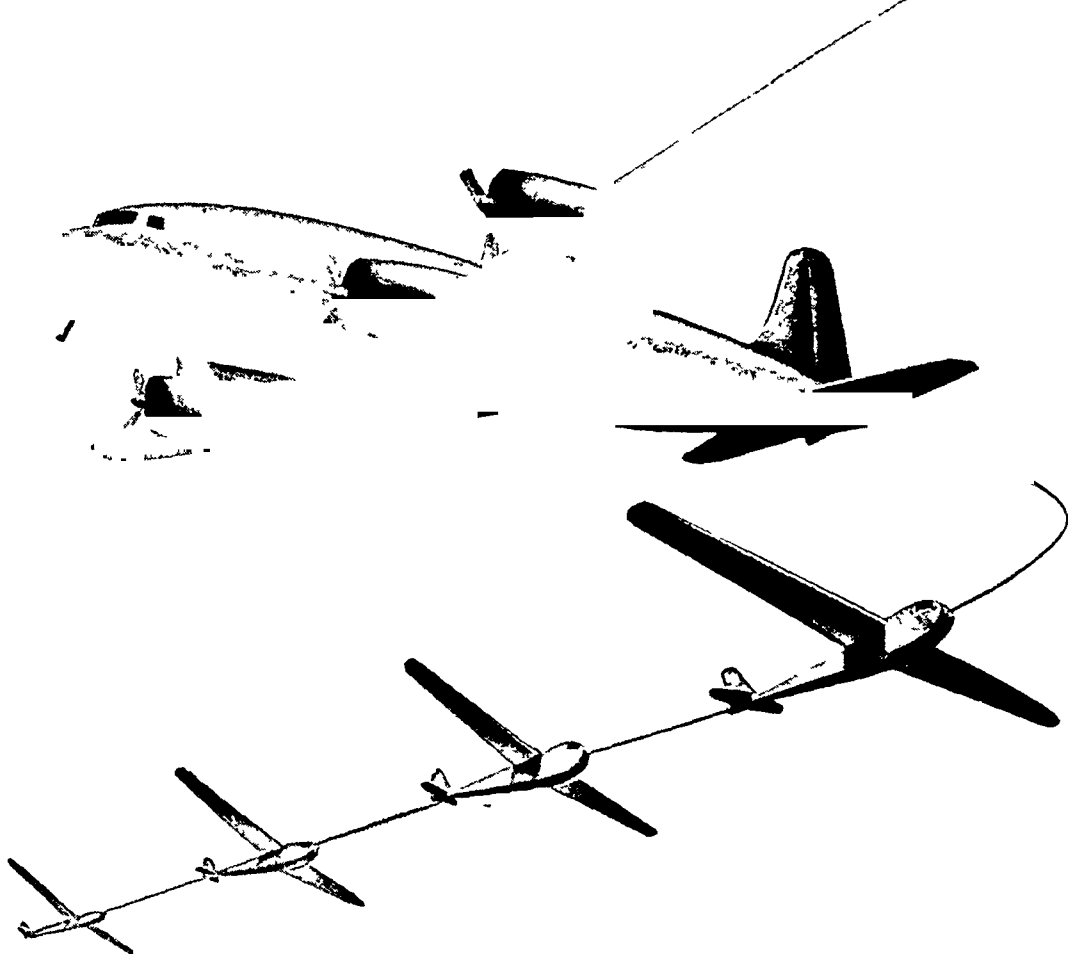
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## Treatment of Adrenal Insufficiency

ROBERT H. WILLIAMS, M.D., JAMES L.  
WHITTENBERGER, M.D., GROSVENOR W.  
HISSELL, M.D., AND ALBERT R. WEIN-  
GLASS,<sup>1</sup> M.D.

*With the Technical Assistance of*  
ELEANOR B. PETERS, B.A.

*From the Thorndike Memorial Laboratory, Second  
and Fourth Medical Services (Harvard), Boston  
City Hospital, and the Department of Medicine,  
Harvard Medical School, Boston, Massachusetts.*

THE INTRODUCTION of desoxycorticosterone for the treatment of Addison's disease was a significant advance in medicine (62). This hormone tends to correct the abnormalities in the salt and water content of the body and, secondarily, other abnormalities, but it does not provide for two of the major functions of the adrenal cortex: (a) gluconeogenesis and (b) androgenic function. Since both of these hormonal effects are eminently concerned with muscle function (see discussion), it is not surprising that many patients with adrenal insufficiency complain of weakness and easy fatigability in spite of adequate doses of desoxycorticosterone.

Corticosterone and allied substances, by their ability to promote conversion of protein to carbohydrate, protect against hypo-

glycemia and depletion of liver and muscle glycogen. In so doing these hormones increase the strength and exercise tolerance of adrenalectomized animals. They have other advantageous effects, such as the prevention of water intoxication. However, the expensiveness of corticosterone has prohibited its prolonged use in adequate quantities in the treatment of adrenal insufficiency.

Since the adrenal cortex secretes androgenic substances, which are concerned with muscle development, it is desirable to investigate the effect of these compounds on Addison's disease. The unavailability of potent androgenic substances of adrenal origin and also the demonstration of the pronounced myosthenic<sup>2</sup> effects of testosterone led to the

<sup>2</sup> The frequent necessity for reference in this paper to the muscle strengthening effect of various chemicals makes it desirable to have one word to express this idea. The word

<sup>1</sup> Dr. Weinglass died January 3, 1945.

use of testosterone in the treatment of the adrenal insufficiency of Simmonds' disease (68). Five patients with this disease were treated with the following four substances: methyl testosterone, testosterone pellets, desoxycorticosterone pellets, and desiccated thyroid. A marked improvement resulted in each patient; the increase in strength was particularly gratifying. In the present report is given the subsequent clinical response of all these five patients with Simmonds' disease, as well as the results of treatment of another such patient; metabolic studies were conducted in two of the patients. The results of

dison's disease was clearly established in 11 cases, with the exception of *Case 4* in which there was some uncertainty about the diagnosis of Simmonds' disease. Five of the patients were males and six were females. In each case weakness was an outstanding complaint. The six patients with Simmonds' disease had lost no significant amount of weight but all five of the subjects with Addison's disease had experienced a distinct loss in weight. The individuals with Addison's disease were markedly pigmented, but there was no significant pigmentation in the other subjects. Nine patients had experienced adrenal crisis

TABLE 1. SIGNIFICANT CLINICAL DATA

Case No.	Etiology	Age Yrs.	Sex	Duration of symptoms. Years	Weakness	Pigmentation	Adrenal crisis	Blood pressure mm. Hg.	Serum sodium m.eq/l	17-Keto-steroids mg./day	Insulin sensitivity	Follicle stimulating hormone R.U./day	B.M.R. Per cent	Plasma iodine $\gamma$ /100 cc.	X-ray of sella turcica
Simmonds' Disease															
1	Postpartum necrosis	42	F	12	++++	0	+	90/50	133	0.3	Incr.	0	-43	1	Neg
2	Chromophobe adenoma	46	M	5	++++	0	+	74/65	127	2.5	Incr.	0	-36	—	Enlargement, destruction
3	Chromophobe adenoma	37	F	5	+++++	0	+	90/60	127	0.4	Incr.	0	-30	—	Enlargement, destruction
4	? Thrombosis	60	F	8	+++	0	+	100/65	136	1.4	Incr.	0	-33	3	Neg.
5	? Syphilis	45	F	20	+++++	0	+	105/75	127	0.2	Incr.	0	-32	—	Neg.
6	Chromophobe adenoma	42	M	1	++	0	0	82/60	—	0	Incr.	0	—	—	Enlargement, destruction
Addison's Disease															
7	?	41	M	1	+++	+++	0	90/60	131	3.1	Incr.	—	-10	7.2	Neg.
8	Tuberculosis	44	M	4	+++	+++++	+	60/40	119	1.0	—	—	-41	2.0	Neg.
9	?	43	F	1	+++++	+++++	+	88/60	130	1.5	Incr.	—	-29	2.8	Neg.
10	?	36	F	1	+++++	+++++	+	80/55	129	0	Incr.	—	-14	—	Neg.
11	? Tuberculosis	38	M	3	+++	+++	+	106/64	133	2.0	Incr.	+	-26	—	Neg.

(96 R.U.)

comparable investigations in five patients with Addison's disease are given; metabolic studies were conducted in four of these cases.

The primary aim of therapy in these cases is the production of marked clinical improvement, as manifested by an increase in the patient's sense of well-being and in his work performance. Such an evaluation is sometimes difficult and requires a long time but some index of the probable effectiveness of the hormones can be readily obtained by estimating their effect on various chemical constituents of the body, as for example, the effect on nitrogen metabolism.

#### METHOD OF STUDY

The diagnosis of Simmonds' disease or Ad-

myosthenic was chosen, the prefix *myo* and the suffix *sthenic* being of Greek origin and meaning *muscle* and *strength*, respectively.

All patients had hypotension and a very small excretion of 17-ketosteroids (table 1). The serum sodium concentration, measured in ten cases, was low in each. In the ten cases in which an insulin tolerance test was performed, insulin sensitivity was found in each. The basal metabolic rate, tested in ten cases, was subnormal in eight. The protein-bound iodine, determined in five patients (including three with Addison's disease), was definitely subnormal in four. Roentgenograms of the sella turcica indicated normal structure in all of the patients with Addison's disease and in three with Simmonds' disease, whereas in three of the latter group there was enlargement and destruction of the sella, which was considered to be due to pituitary tumor. As far as could be ascertained, none of the patients had any primary disease of the kidney, liver, gastro-intestinal tract or any other site.

which would interfere with the metabolic studies

Observations were made of the effects of methyl testosterone,<sup>3</sup> testosterone pellets and intramuscular injections of testosterone propionate. The effects of androstanediol, methyl androstanediol, and stilbestrol dipalmitate were also studied, the last one having been shown to increase the glycogen content of the liver. We wished to learn the effects of these substances in patients who were treated optimally with desoxycorticosterone, in those given inadequate doses, and in others given none. Some patients were given several different hormonal preparations, with only short intervals between, in order that the effects might be compared in the same individual when the disease was in approximately the same stage.

All metabolic balance studies were performed with the patients in a special ward in the hospital. The individuals were not confined to bed. No restriction of the fluid intake was imposed. The diet was usually the same each day throughout the period of study, although in some instances two isocaloric diets were given on alternate days. The elements of the diet were obtained in large quantities before the balance studies were begun, in order to help insure a uniform intake of food. Extra sodium chloride, usually in 4 gm. amounts, was given daily and the patient was required to take all of it regardless of the desires of his appetite. The balance study was not begun until the patient had been on the standard regimen for from 5 to 12 days. Urine specimens were saved in 24-hour amounts, with glacial acetic acid as a preservative except when specimens were collected for the estimation of the 17-ketosteroids, in this event concentrated hydrochloric acid was used.

<sup>3</sup> The methyl testosterone (Metandren) used was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J. This company also supplied perlingual methyl testosterone (Metandren Linguets), pellets of desoxycorticosterone acetate (each weighing approximately 125 mgm.), androstanediol 3 $\alpha$ , 17 $\alpha$ , methyl androstanediol 3 $\alpha$ , 17 $\alpha$ , and testosterone propionate (Perandren). The pellets of testosterone (Oreton T) were supplied by the Schering

Blood was drawn from the fasting patient during the morning the regimen was to be changed.

Estimations were made of the excretion in the urine of sodium,<sup>4</sup> chloride, potassium, nitrogen, creatine, creatinine and 17-ketosteroids. Changes in the concentration in the blood of sodium, chloride, potassium, sugar, non-protein nitrogen, and carbon dioxide combining power were estimated in most cases. Insulin tolerance tests were conducted in all but one patient.

Daily estimations of the blood pressure, weight and strength were made, the last being tested with a hand dynamometer.

#### RESULTS OF STUDY

*Case 1 (no 1047166) H O*, a housewife, aged 42, was admitted to the hospital in May, 1941. The history, physical examination and laboratory studies were those of a classical example of panhypopituitarism, the onset having been associated with a stormy post-partum course 12 years previously. In December, 1941, therapy with methyl testosterone, desoxycorticosterone acetate, and desiccated thyroid was started. After several weeks two pellets of testosterone, 150 mg. each, and a pellet of desoxycorticosterone were implanted. Thyroid was given in doses of 64 mg. daily.

With this therapy there was a remarkable improvement in the general appearance, energy, strength and sense of well being of the patient, the changes having begun to appear within a few days after the institution of the combined therapy and continuing for several months. The eyebrows, as well as the hair on the scalp, axillae, arms and pubis showed moderate growth. The blood pressure, previously low, was maintained at a normal level. Anorexia and the occasional attacks of nausea, vomiting and abdominal cramps disappeared, although she continued to experience an occasional episode of hypoglycemia in spite of eating frequently throughout the day. Most of the manifestations of myxedema disappeared. No complications from the therapy resulted, other than the appearance of a small amount of fuzzy hair on the cheeks and upper lip.

<sup>4</sup> The methods used for the analyses are as follows: sodium, Butler and Tuthill (8) as modified by Consolazio

Butler and MacLachlan (59), total serum protein, Kagan

During the year following the implantation of the pellets the patient was seen at monthly intervals. After about from eight to ten months a slight reduction in strength began to appear. Her friends observed a "slowing-up" in her mental and physical activities, in spite of the fact that she continued to

133 gm. of carbohydrate, 53 gm. of fat; there 33 m.eq. of sodium and 28 m.eq. of potassium. low-calorie diet was chosen by the patient as she not feel confident of eating more than this amount. After a period of standardization and two cycles periods of four days each, testosterone propionate

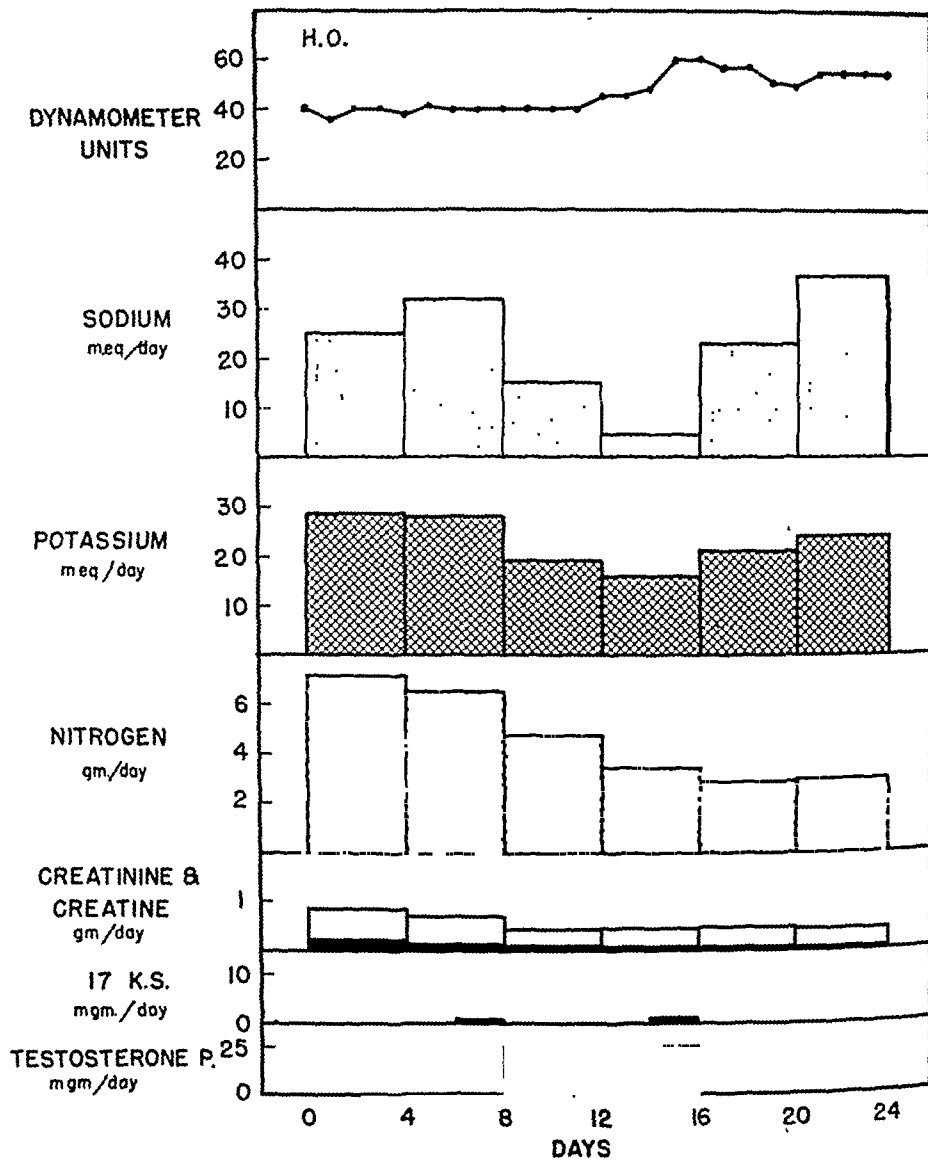


FIG. 1. Response in Case 1 to treatment with testosterone propionate while the patient was maintained on a constant diet. The strength was measured with a hand dynamometer. In the columns are recorded the average daily excretion in the urine of sodium, potassium, nitrogen, creatinine and creatine. The excretion of 17-ketosteroids (17 KS) is also charted.

take 64 mg. of thyroid daily. Puffiness of the skin returned. All of the axillary hair and most of the pubic hair disappeared again. She became weak, dizzy and vomited once. After three days of moderate weakness she returned to the hospital, in April, 1943, one year after the pellet therapy was started. The same dosage of desiccated thyroid was continued and she was placed on a diet containing 1400 calories per day, in the proportions of 54 gm. of protein,

was given intramuscularly in doses of 25 mg. per for eight days, followed by two similar periods out treatment. During the intervals of treatment for several days thereafter a marked improvement the patient resulted. She experienced an increased appetite, energy, strength and feeling of well-being. Dynamometer estimations showed about a 30 per cent increase in strength (fig. 1) which persisted at least eight days after discontinuation of the

1943. No change in the weight resulted and the blood pressure remained normal. Testosterone propionate caused a pronounced retention of sodium, potassium, nitrogen, and creatinine, which persisted for a number of days after cessation of treatment. Essentially no change resulted in the excretion of 17-ketosteroids in the urine.

Since no pellets of testosterone were available, she

In January, 1944, she was brought into the hospital in a semi stuporous state, she had developed pneumonia in the left lower lobe. She had voluntarily discontinued the thyroid and methyl testosterone therapy one month previously. Two weeks before admission she developed a rhinitis and bronchitis. When suffering from respiratory infections she had previously cooperated by taking an additional 4 gm.

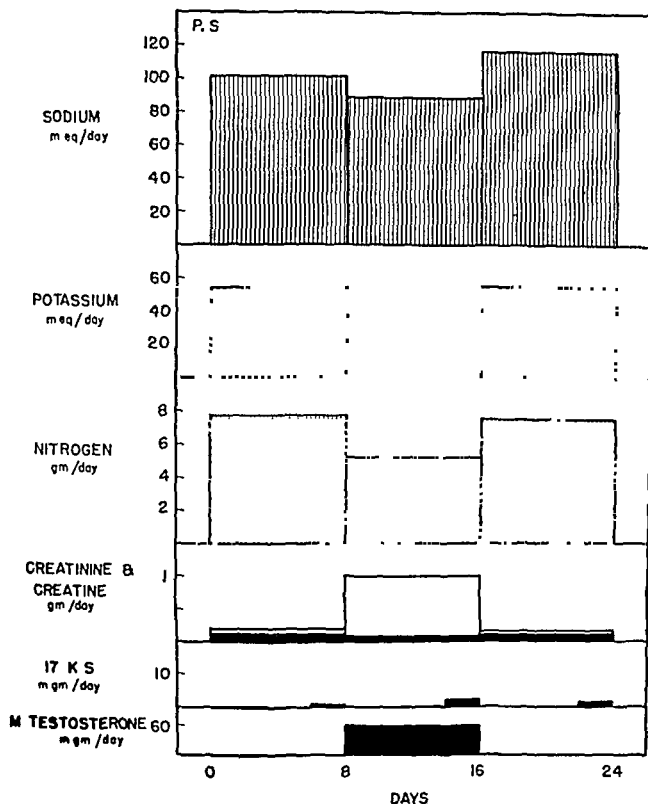


Fig 2 Response in Case 2 to treatment with methyl testosterone

was discharged from the hospital in May, 1943, after a period of 10 days. With this treatment, the patient's condition improved. In September, 1943, one pellet of desoxycorticosterone acetate was implanted. In October she discontinued the methyl testosterone therapy, following which she noticed a decrease in strength and energy, but with resumption of this therapy, in November, she experienced a distinct improvement.

of sodium chloride daily, but she disregarded the prescription on this occasion. On admission her blood pressure was 90/60. The temperature was 102.4°. In spite of treatment with adrenal cortical extract, desoxycorticosterone, testosterone propionate, sulfathiazole, frequent infusions of glucose and saline, and general supportive measures the patient died four days after admission.

At autopsy the pituitary gland was found to be



very small and it was composed almost entirely of fibrous tissue with a very few nests of basophilic acini and some colloid-filled cysts. A small portion of the pars nervosa was present. The thyroid gland was quite small; it consisted chiefly of fibrous tissue with a few small follicles relatively devoid of colloid. Extensive search failed to reveal the presence of the adrenals. The ovaries were small and fibrotic. The pancreas and the parathyroid glands were not remarkable.

*Case 2 (no. 1047262).* P.S., a white laborer, aged 46, was admitted to the hospital in August, 1941. The history and physical examination suggested that he had Simmonds' disease, and the laboratory data gave strong support to this diagnosis. A chromophobic adenoma was regarded as the probable cause of the disease and roentgenotherapy was applied to the pituitary region. In December, 1941, he began the treatment with desiccated thyroid, desoxycorticosterone acetate and methyl testosterone. The marked improvement in the ensuing weeks prompted the implantation of five pellets of desoxycorticosterone acetate and three pellets of testosterone, each of the latter weighing 150 mg. The remarkable improvement in the ensuing few months has already been reported (68). He was subsequently seen in the Out-patient Department at intervals of from one to two months.

In September, 1942, he began to notice a slight decrease in strength; however, upon taking 30 mg. of methyl testosterone daily he regained some of his former vigor.

In March, 1943, he was readmitted to the hospital for study. His general condition was good, and he was fed a diet yielding 1916 calories, composed of 85 gm. of protein, 160 gm. of carbohydrate, 104 gm. of fat, 120 m.eq. of sodium and 55.6 m.eq. of potassium. After a control period of eight days he was given 60 mg. of methyl testosterone, divided into three doses daily for eight days. A distinct increase in strength and energy was noted two days after the therapy was started. There was retention of sodium (fig. 2), potassium and nitrogen, and there was a marked increase in the amount of creatinine excreted. No significant effect on the creatine or the 17-ketosteroid excretion was observed. There was no change in the patient's weight; the blood pressure remained normal.

In the spring of 1943, and during the subsequent year and a half, his therapy in addition to the 96 and 128 mg. of thyroid was methyl testosterone in doses of 30 mg. daily; extra salt was added as indicated during respiratory infections and also during the summer. Intervals of two to three months elapsed when he was financially unable to secure the methyl testosterone. During each of these periods there was a definite decrease in strength, energy, and ambition, but on each occasion there was a rapid amelioration of symptoms following the resumption of therapy. However, not as much improvement resulted with

doses of 30 mg. as with 50 or 60 mg., nor did he feel quite as well with the latter as during the four or five months after the implantation of the three pellets of testosterone, mentioned above.

In February and March, 1944, he occasionally felt dizzy, weak, and complained of anorexia. There was also a slight drop in his blood pressure. These changes persisted in spite of 4 to 8 gm. of extra sodium chloride daily and methyl testosterone, 30 mg. daily. In April, 1944, two pellets of desoxycorticosterone, 125 mg. each, were implanted; a distinct improvement in the patient resulted. Within a few weeks edema developed, but this disappeared with the cessation of sodium chloride therapy. In October, 1944, three pellets of testosterone, 75 mg. each, were implanted.

During the three years of treatment the patient had gained 25 pounds in weight. The visual field, which were narrowed at first, are now normal. There has been no apparent destruction of the sellae turcica; he has maintained a moderately heavy beard and some axillary and pubic hair which developed in association with androgen therapy, and he has performed a moderate amount of work.

*Case 3 (no. 1048285).* D.N., a female artist, aged 37, was admitted in May 1941. She was regarded as having Simmonds' disease resulting from a chromophobe adenoma. Her therapy was similar to that outlined in the two previous cases; essentially all of the results were reported previously (2). After having apparently been in very good general condition until the day of her death, she died at home after an illness of a few hours about six months after therapy was started. The cause of death was apparently a hypoglycemic reaction, but no opportunities were afforded for diagnosis either by clinical measures or by necropsy.

*Case 4 (no. 1058888).* I.D., an unmarried white woman, aged 60, was admitted to the hospital in January, 1942. She had been treated for the previous eight years for myxedema and pernicious (?) anemia. The patient was diagnosed as having Simmonds' disease on the basis of the following: the picture of myxedema, which had not responded satisfactorily to prolonged treatment with thyroid; the hyper sensitivity to insulin; the small quantity of 17-ketosteroids excreted in the urine; the low concentration of serum sodium; a negative test for follicle-stimulating hormone in the urine (tested for 20 R.U. per 2 hours); and the clinical manifestations of adrenal insufficiency. She was treated with 92 mg. of desiccated thyroid daily, two pellets of desoxycorticosterone acetate and one of testosterone (150 mg). She experienced a marked general improvement with a distinct increase in strength. However, within a month the development of dyspnea and hypertension led to the removal of one of the desoxycorticosterone pellets. The dyspnea and hypertension diminished, but within another two months the blood pressure had risen to 190 mm. systolic and 100 mm. diastolic, and there was moderate dyspnea.

consequently, the remaining pellet of desoxycorticosterone was removed. Improvement of the patient was apparent within a few days, but one month later she developed manifestations of a cerebral thrombosis signs of which subsided in a few days. Throughout the last two years she has been seen at intervals of one to two months. Aside from headaches, slight dyspnea and episodes suggesting hypoglycemia, she has felt relatively well. She developed fairly good strength and a normal amount of axillary and pubic hair. In September, 1944 she was admitted to the hospital for reevaluation. Although she had had no thyroid treatment for ten weeks, she had no definite evidence of myxedema and her basal metabolic rate was  $-3$ . Her insulin tolerance test, performed in the same manner as in 1942, showed distinctly less insulin sensitivity than earlier. The 17 ketosteroid excretion which was 1.4 mg per 24 hours in 1942, was 3 mg. Her FSH test, which was negative to 20 R.U. in 1942, was positive. The "water test" was positive. Therefore the patient showed a definite improvement in her glandular functions.

Case 5 (no 764228) F.S., a housewife, aged 45, as admitted to the Massachusetts Memorial Hospital in December, 1941. After the diagnosis of Simmonds' disease was established her therapy was 2 mg of desiccated thyroid daily and the implantation of two pellets each of desoxycorticosterone and testosterone propionate. She experienced general well-being here occurred.

She lost strength. She did not return for observation very often, but continued taking thyroid regularly. In November, 1943, she was admitted to the Boston City Hospital for replenishment of therapy. She exhibited many features of chronic adrenal insufficiency. She was given 2 mg of desoxycorticosterone acetate daily. After one week the dosage was reduced to 1 mg and she was also given 25 mg of testosterone propionate three times per week. Although some improvement was apparent within two days after the desoxycorticosterone therapy was started, there was a marked increase in strength and energy within a few days after the testosterone was instituted. Unfortunately, two weeks after the latter therapy was started she developed virus pneumonia and died within 24 hours.

At autopsy the pituitary was found to be very small. On microscopic examination there were found few acidophilic, basophilic and chromophobic cells scattered in dense scar tissue. No etologic lesions in the pituitary were observed. The thyroid gland was about one half the normal size, the acini were atrophic. The adrenals were completely replaced by fibrous tissue. There was bronchopneumonia in each lower lobe.

We are very grateful to Dr. Chester S. Keefer and his staff for their generous cooperation in the study of Cases 9 and 11.

Case 6 (no 111478) G.M., a laborer, aged 42, was admitted to the hospital in June, 1943. He was found to have Simmonds' disease, which was apparently due to a chromophobe adenoma of the pituitary gland. Following an unsuccessful attempt to remove the tumor, roentgenotherapy was applied. There was no improvement in his endocrine functions, but there was some improvement in his visual fields. Beginning in March, 1944, he was given intramuscularly 25 mg of testosterone propionate three times a week for six weeks. No other hormonal therapy was given.

During this treatment there was a marked increase in strength and a slight gain in weight. Pellets of testosterone are to be implanted.

Case 7 (no 1102778) J.C., a retired fireman, aged 42, was admitted to the hospital in April, 1942, with Addison's disease, which he apparently had had for more than a year.

On the day after admission he began receiving desoxycorticosterone acetate intramuscularly, and this was given daily until the amount necessary to maintain the patient in good condition was ascertained. Four pellets of desoxycorticosterone acetate were implanted on July 6th.

Four pellets of testosterone, 75 mg each, were implanted on April 30th. On the day preceding this treatment the 17 ketosteroid excretion was 2.5 mg, on May 14th it was 2.6 mg and June 17th it was 1.7 mg. On the first of June he began to take 64 mg of desiccated thyroid daily.

With the foregoing treatment he experienced a marked improvement, but it was, of course, difficult to assess the value of each of the drugs used.

Following discharge from the hospital, in July, 1942, he was seen every one to two months in the Outpatient Department. At all times he was in good condition and was taking care of miscellaneous jobs satisfactorily. However, he sometimes had vague complaints, thought to be psychoneurotic. He also showed a lack of stamina.

In April, 1943, he was readmitted to the hospital for a check up. He was found to be in relatively good condition, having no significant complaints, a normal blood pressure, good strength, and a normal concentration of serum sodium.

He was placed on a diet consisting of 2031 calories with 87 gm of protein, 178 gm of carbohydrate, 102 gm of fat, 56 m eq of potassium and 120 m eq of sodium. After a period of stabilization for five days and a control period of four days he was given intramuscularly 25 mg of testosterone propionate daily for eight days. With this therapy there was no definite increase in strength and no change resulted in the hand dynamometric estimations, both before and during therapy. The readings were 100 to 110, which gives evidence that his strength was as good as that of a normal man. During treatment there resulted a distinct retention of sodium (fig. 3), a slight retention of potassium, and a marked increase in the amount of 17 ketosteroids excreted. No signifi-

cant changed resulted in the creatine, or creatinine, excretion, but there was a slightly increased excretion of nitrogen.

His general condition was sufficiently good to warrant a delay in the replenishment of the pellets of desoxycorticosterone until January, 1944. He has remained in good condition and has been performing a moderate amount of work.

monthly intervals. He gained 10 to 20 pounds; weight and became stronger; his blood pressure remained essentially normal. Although he occasionally had spells of weakness and dizziness, most of the time he felt quite well. His muscular development, good state of nutrition and general appearance suggested that he should have the capacity for almost any type of work. He tried several jobs but did not

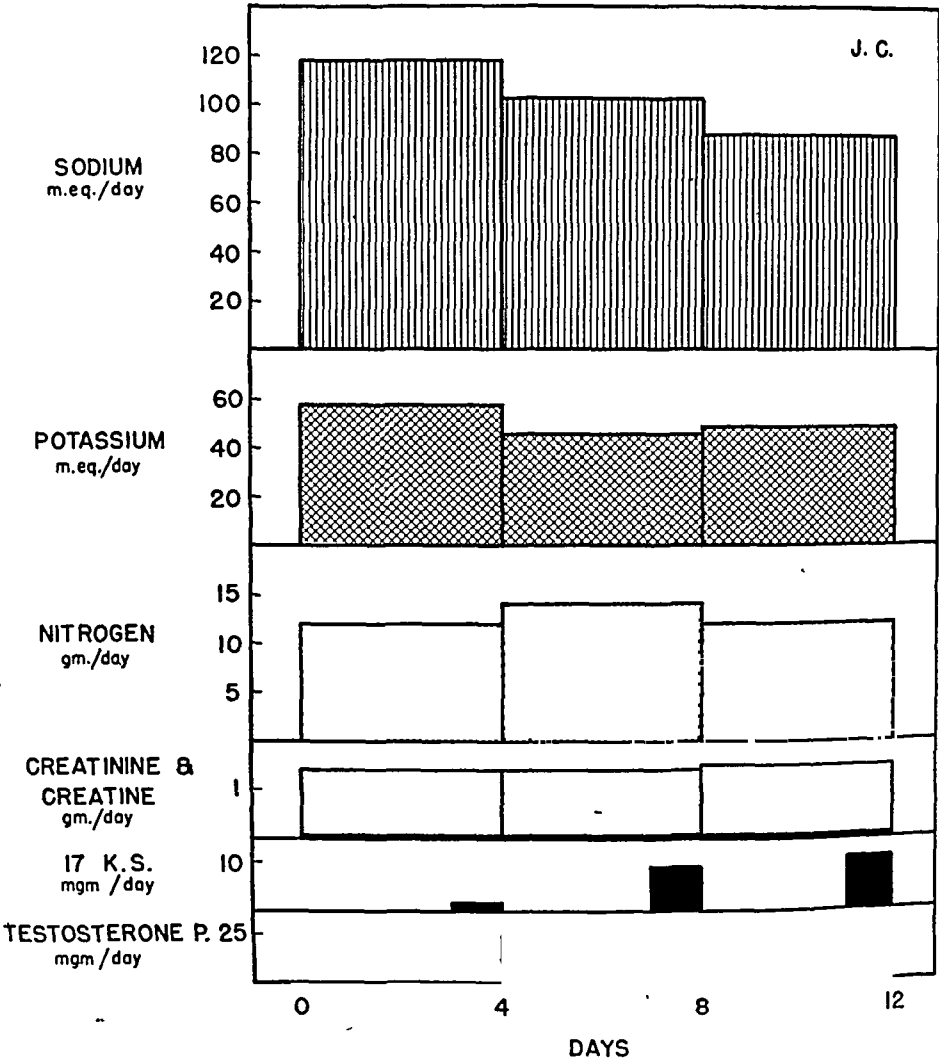


FIG. 3. Response in Case 7 to treatment with testosterone propionate.

*Case 8 (no. 1080075).* C.E., a laborer, aged 44, was admitted to the hospital in an Addisonian crisis in February, 1941. He had a history of Addison's disease for about four years or longer. Roentgenograms revealed the presence of calcification in the adrenals and many scattered plaques in the lungs, but no evidence of active tuberculosis. After several weeks of treatment with extra salt and intramuscular injections of desoxycorticosterone, four pellets of desoxycorticosterone were implanted. He was discharged from the hospital in April, 1941, and in the following year was seen in the Out-patient Department, at

continue with any for longer than a few days or weeks. He stated that the work was "too hard" and that he soon became tired.

In June, 1942, he complained of having lost 15 pounds in weight in the two previous months. His strength also decreased. With the administration of 8 gm. of extra sodium chloride per day his symptoms definitely improved.

In August, 1942, he was readmitted for further study and treatment. At this time he had no complaint other than increased weakness in the previous month. His blood pressure was normal, as was the

rum sodium and potassium, but the 17-ketosteroid excretion was only 4 mg. per 25 hours. Two pellets of testosterone, 150 mg. each, and two pellets of desoxy-epiandrosterone acetate were implanted. Estimation of creatinine and nitrogen excretion for ten days before and 10 days during the testosterone treatment showed no change in the former and only slight re-

His blood pressure was 100 mm. systolic and 70 mm. diastolic. The hematocrit, non-protein nitrogen, and fasting blood sugar were normal, but the serum sodium was 135 m.eq. per liter and the chloride 87 m.eq. per liter. The serum potassium was 4.7 m.eq. per liter.

He was fed on a diet calculated to yield 1937

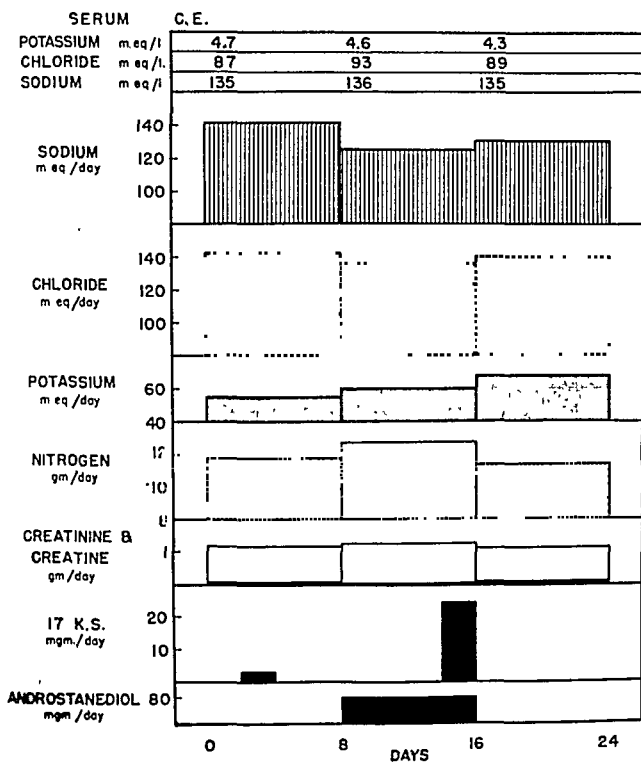


FIG. 4. Response in Case 8 to treatment with androstanediol, 3 $\alpha$ , 17 $\alpha$ .

tion of nitrogen. During the ensuing few weeks he felt stronger and better in general than he had felt before. About one month after the pellet treatment he developed slight edema, but this disappeared with elimination of extra sodium chloride.

His progress continued to be good until August, 1943, when he noticed more weakness than usual. His blood pressure was slightly low. However, definite improvement resulted with salt therapy.

In January, 1944, he was readmitted for study and further treatment. He had no specific complaints, other than a tendency for easy fatigability.

calories, composed of 88 gm. of protein, 80 gm. of fat, 217 gm. of carbohydrate, 137 m.eq. of sodium, and 95 m.eq. of potassium. After 12 days a control period of eight days was run after which he was given 20 mg. of androstanediol four times daily for eight days. This was followed by another control period for eight days. In association with the treatment no changes resulted in the normal blood pressure, weight, or dynamometric estimations. However, a few days after the institution of therapy the patient felt somewhat stronger.

The androstanediol caused a retention of sodium

(fig. 4) and chloride but an increased elimination of potassium, nitrogen and creatinine. It produced a marked increase in the elimination of 17-ketosteroids. No significant change occurred in the values of the serum electrolytes.

On the completion of the metabolic study two pellets of desoxycorticosterone acetate were implanted. One month later five pellets of testosterone, 75 mg. each, were inserted. He obtained a job and

for the next three months she was about 5 gm. of extra sodium chloride daily and 6 mg. of desoxycorticosterone. In December, while the patient continued to receive the foregoing treatment, the effects of methyl testosterone studied. She was fed a constant diet; 60 mg. of methyl testosterone were given daily for 10 days, followed by 30 mg. for 12 days. Associated with therapy there was a definite increase in the pati

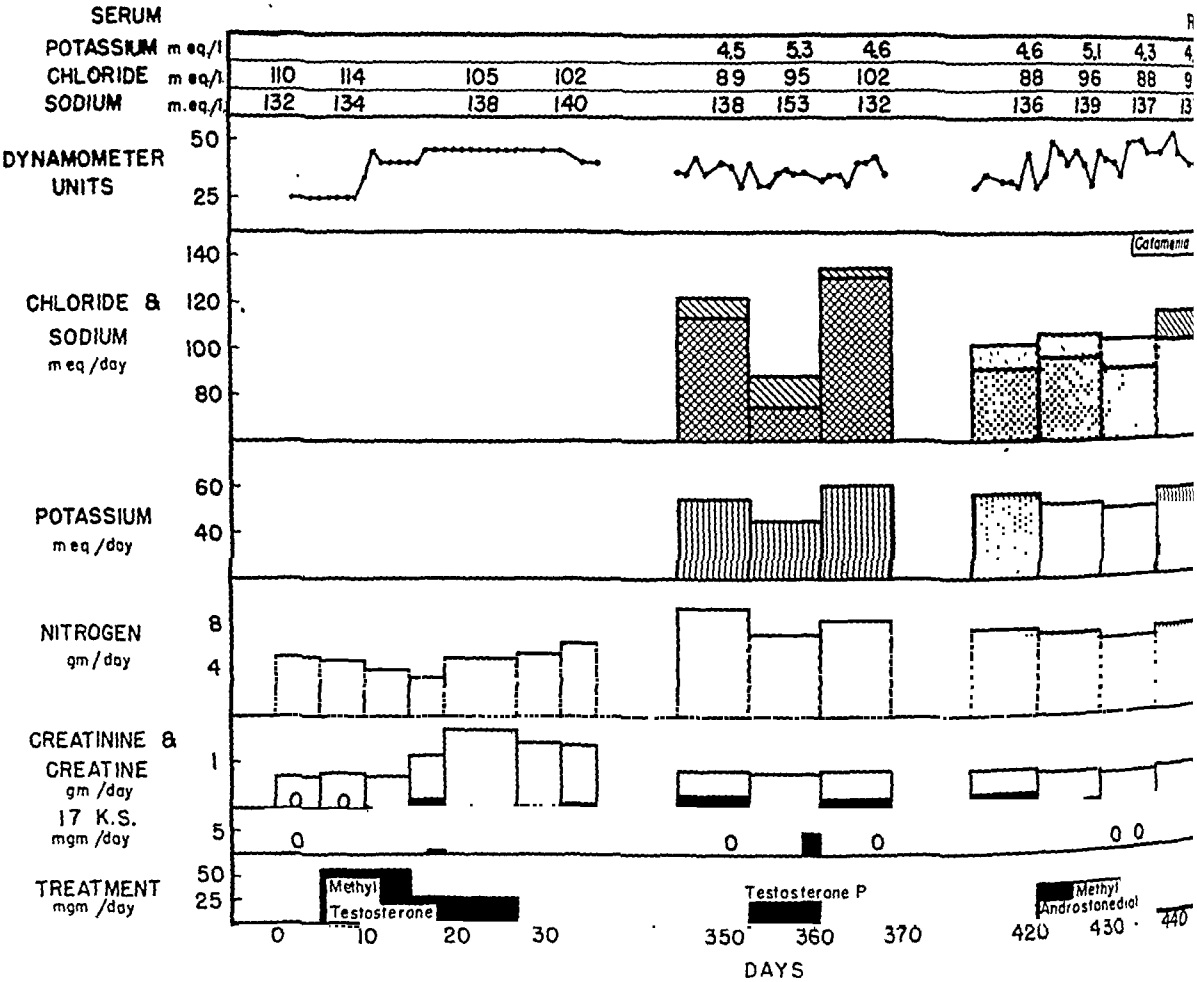


FIG. 5. Response in Case 9 to treatment with methyl testosterone, testosterone propionate, and methyl androstenediol, 3 $\alpha$ , 17 $\alpha$ .

has now worked regularly for the past seven months, this being the longest interval of work in four years. During this time he has felt quite well and has had more strength than he has had at any other time in the last four or five years. He has maintained a normal blood pressure, weight and serum sodium concentration.

Case 9 (no. 1125208). R.S., a housewife, aged 43, was admitted to the Massachusetts Memorial Hospital in September, 1942. She had shown manifestations of Addison's disease for about one year. The etiology of the disease was not known; there was no evidence of tuberculosis.

Within a few days after admission to the hospital she began receiving treatment for adrenal insufficiency.

strength, subjective and objective (fig. 5). The therapy caused a retention of nitrogen, but an increased elimination of creatinine and creatine. The serum sodium concentration increased, but there was no significant change in the 17-ketosteroid excretion. Following this balance study four pellets of desoxycorticosterone were implanted. However, about two weeks later the patient developed hypertension and subcutaneous edema which persisted in spite of sodium chloride restriction. The removal of one pellet corrected these complications.

Following discharge from the hospital in February 1943, she was seen at monthly intervals. She was fairly well and did a moderate amount of housework. She maintained a normal blood pressure

rum sodium, but at each visit she complained of weakness, easy fatigability and lack of energy.

In November, 1943, she was admitted to the Boston City Hospital for further treatment which was directed toward an improvement of her strength for clinical condition and serum sodium concentration were found to be relatively well regulated. She was fed a constant diet yielding 1577 calories, composed of 71 gm of protein, 201 gm of carbohydrate, 4 gm of fat, 118 m eq of sodium and 81 m eq of potassium. Eight days were allowed for stabilization and another eight days, for a control period. Following this 25 mg of testosterone propionate were injected, intramuscularly, daily for eight days. Within 40 or three days after this therapy was started the patient experienced a distinct increase in strength and energy as evidenced not only by her assertions but also by her activities on the ward. However, the dynamometric estimations revealed no significant change. During this therapy there was a marked retention of sodium and chloride. There was a moderate retention of nitrogen, potassium, and creatine. The 17 ketosteroid excretion changed from 0 to 5 mg per day.

After the patient became stabilized she was given, intramuscularly, 10 mg of stilbestrol dipalmitate daily, but after five days she was so sick that this therapy was discontinued. She developed nausea, vomiting, nervousness, hyperhidrosis and marked weakness. No change resulted in the excretion of sodium, chloride, nitrogen, creatine, or creatinine, but there was a slight retention of potassium. No 17 ketosteroids were excreted. Following this treatment about two weeks were required for the patient to return to her former condition. After this readjustment she was given, intramuscularly, 1 mg of desoxycorticosterone acetate daily.

In order to study the effects of methyl androstenediol, she was again placed on a constant diet calculated to yield 1362 calories, composed of 65 gm of protein, 160 gm of carbohydrate, 51 gm of fat, 107 m eq of sodium and 75 m eq of potassium. After a period of five days of standardization and a control period of eight days she was given 10 mg of methyl androstenediol four times daily for 16 days. During this therapy there was a definite increase in strength, subjective and objective (fig. 5). There was slight retention of potassium, nitrogen, creatinine and creatine, but no significant alteration in the excretion of 17 ketosteroids, sodium or chloride.

Twelve days after cessation of treatment with methyl androstenediol, one pellet of desoxycorticosterone acetate and three pellets of testosterone, 5 mg each were inserted.

She was discharged from the hospital on April 5, 1944. When next seen, on the first of June, she stated that her strength and energy were greater than before the hospitalization, but there was not as much improvement as was desired. For a period of six weeks, beginning the first of June she was given daily 40 mg of androstenediol. During this period

of therapy there was a further increase in strength and in her sense of well being. From July 15th to August 15th no additional treatment was given. The patient thought that there was a very slight loss of strength in this interval. During the latter half of August she was given 80 mg daily of methyl androstenediol, without any definite effects. No extra therapy was administered from September 1st to October 15th, but during the subsequent month she was given daily 50 mg of methyl testosterone linguets. There was only a slight increase in strength and energy associated with this.

*Case 10 (no 1124320) S F*, a housewife, aged 36, was admitted to the hospital in November, 1943. She had shown manifestations of Addison's disease for about seven months, she had not had any specific treatment. Five days before the metabolic study was started she was fed a constant diet calculated to yield 1420 calories, composed of 60 gm of protein, 167 gm of carbohydrate, 55 gm of fat, 118 m eq of sodium and 65 m eq of potassium. During a period of three months the effects of testosterone propionate, stilbestrol dipalmitate, androstenediol, and methyl androstenediol were tested. In this case it was decided to use a minimal amount of desoxycorticosterone acetate, in order to note the specific effect of the various drugs. However, it is to be emphasized that the kidney function was impaired more than it is in well treated cases of Addison's disease. On the day that the constant diet was started, the patient began receiving intramuscular injections of desoxycorticosterone acetate, 1 mg daily. At the end of the seventh metabolic period the dosage was doubled.

Testosterone propionate was given, intramuscularly, in doses of 25 mg daily for eight days. The therapy was associated with a distinct increase in the energy and strength of the patient. There was a decrease in the blood non protein nitrogen, a slight increase in the excretion of sodium and chloride, and a slight retention of potassium, nitrogen, creatine and creatinine (fig. 6). No 17 ketosteroids were found in the urine preceding treatment, but with therapy there were 3.6 mg per day.

Nine days after the cessation of testosterone propionate, 5 mg of stilbestrol dipalmitate was given, intramuscularly, daily for six days. Two days after this therapy was started the patient complained of anorexia, nausea and pronounced weakness. These symptoms progressively increased and persisted for several days after the last injection. There was an increased excretion of sodium, chloride, nitrogen and creatine. At the time that the stilbestrol treatment was discontinued, a short insulin tolerance test, using 4 units of insulin intravenously, yielded blood sugar values as follows: fasting, 81 (mg/100 cc) 30 min, 70 and 60 min, 71. When the same test had been conducted one month previously using 3 units of insulin the values were: fasting, 94, 30 min, 50, and 60 min, 62.

Ten days after cessation of the stilbestrol treatment, androstanediol was given, orally, in doses of 10 mg., four times daily for 16 days. About five days after the beginning of this therapy there was a definite increase in strength, subjective and objective (fig. 6). The patient displayed more energy than usual. The androstanediol did not cause any retention of sodium, chloride or potassium and caused no

also had primary hypogonadism, having had features of this condition most of his life. During adolescence he was obese, particularly in the middle third of his body. He never developed axillary or pubic hair or beard. On examination his voice was found to be high-pitched and he was effeminate in his reaction. The arms and legs were long in proportion to the trunk; the testes and penis were small. There was

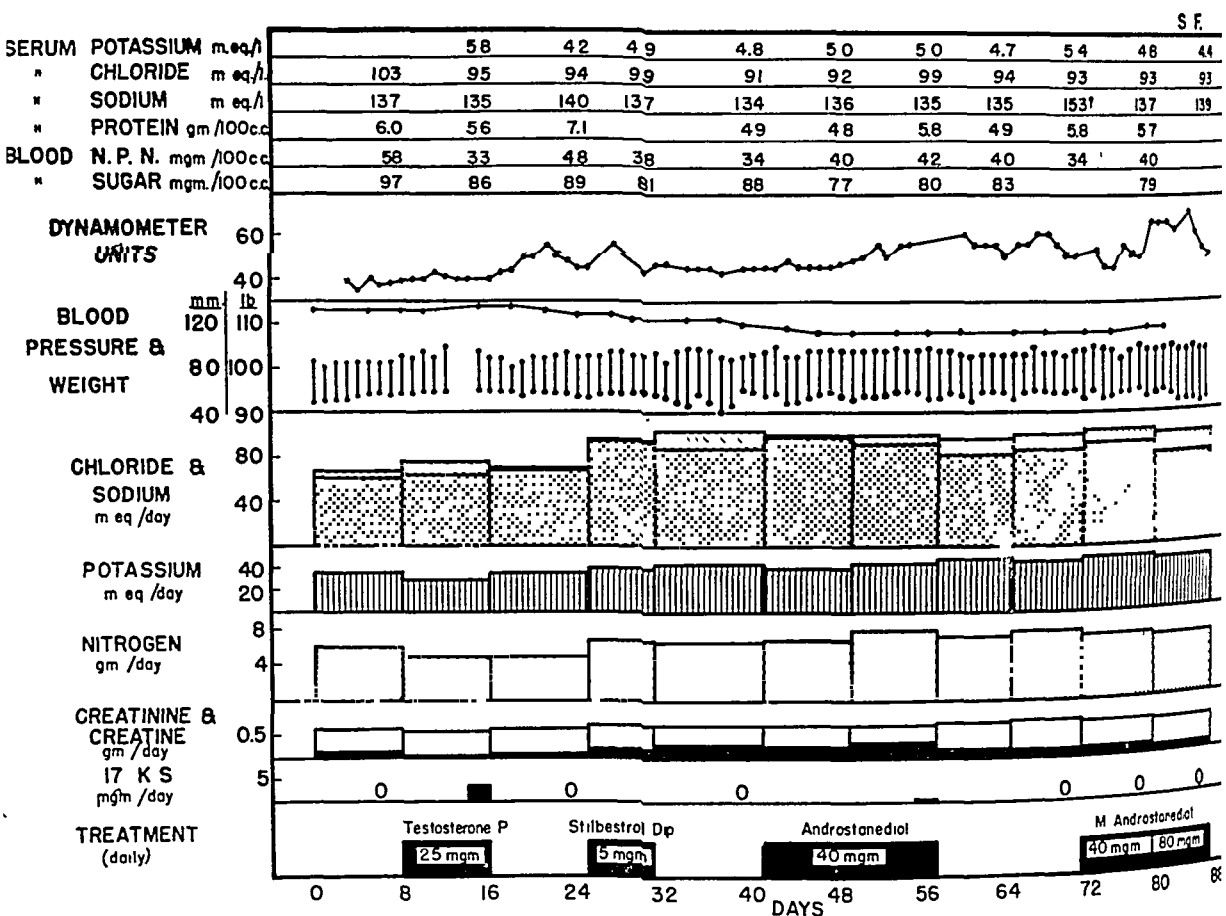


FIG. 6. Response in Case 10 to treatment with testosterone propionate, stilbestrol dipalmitate, androstanediol, 3 $\alpha$ , 17 $\alpha$ , and methyl androstanediol, 3 $\alpha$ , 17 $\alpha$ .

significant increase in the 17-ketosteroid excretion. After an interval of 14 days without treatment the patient was given 10 mg. of methyl androstanediol four times daily for eight days and then 20 mg. four times daily for another eight days. With this therapy there was an increase in strength, subjective and objective, but no significant change in the excretion of sodium, chloride, nitrogen, creatine, creatinine or 17-ketosteroids. Throughout the entire period of study the blood pressure remained low and there was slight loss of weight.

On the completion of these studies four pellets of desoxycorticosterone were implanted.

Case 11 (no. 291751). C.R., a laborer, aged 38, was admitted to the Massachusetts Memorial Hospital in June, 1943, with Addison's disease, having had manifestations of this disorder for three years. He

96 rat units of follicle stimulating hormone in the urine per 24 hours.

After his condition had become somewhat stabilized by treatment with 8 gm. of sodium chloride daily, he was given 20 mg. of methyl testosterone three times daily for three days and then 10 mg three times daily for seven days. During this treatment he gained five pounds, while in the previous week he had not gained. He also observed a definite increase in strength. About two weeks after cessation of the methyl testosterone therapy two pellets of testosterone, 75 mg. each, were implanted subcutaneously. The patient gained four pounds in the next five days, whereas he had not gained in the previous week; he also noted an increase in strength. He was discharged from the hospital in August, 1942, but follow-up studies were unsatisfactory.

## DISCUSSION

In well defined cases of Addison's disease and Simmonds' disease the structure and functions of the adrenal glands are markedly reduced; this leads to a large number of abnormalities which may be clinically apparent. Most of the changes produced are presumably due to decrease in the steroids which are concerned with: (a) control of salt and water balance, (b) androgenic function, and (c) gluconeogenesis. All three factors would seem to be of importance in obtaining maximal performance of muscles. However, the question arises as to the relative importance of each factor. Although certain steroids isolated from the adrenal have predominantly one of the three actions mentioned, some direct or indirect effect on the other functions are also manifested.

Thorn and associates (62) found that with the use of desoxycorticosterone in the treatment of Addison's disease there resulted: (a) an increase in body weight; (b) an elevation of blood pressure; (c) an increase in plasma volume; and (d) a restoration of plasma concentration of sodium, chloride, and potassium to normal levels. With these changes there occurs: (a) an improvement in the absorption of substances from the gastro-intestinal tract, (b) a slight increase in the basal metabolic rate, and (c) an improvement in strength and well-being.

In spite of the beneficial effects of desoxycorticosterone the patients tend to complain of weakness and easy fatigability, even when receiving optimum treatment with this hormone. They also exhibit a deficient capacity to make adequate readjustments in the face of trauma, infections, or radical changes in salt and water metabolism (58). Moreover, they may die of hypoglycemia. Therefore, it is desirable to administer additional therapy; in this connection androgen therapy is now considered.

Although there is not much direct proof that the adrenal cortex produces androgens in normal individuals, there is a great deal of indirect evidence that such is the case (44). Furthermore, in individuals with adrenal

neoplasms large quantities of androgens have been found in the urine.

Reichstein (51) obtained adrenosterone from the adrenal cortex, and Mason and associates (49) prepared the same substance by the oxidation of Kendall's Compound E. In rats and mice gonadectomy causes adrenal hypertrophy in the male, although atrophy results in the female. This hypertrophy is associated with androgenic secretion from some source as evidenced by the continued development of the prostate in the immature castrated rat. If the adrenals are also removed the prostate does not develop. The characteristic x-zone in the adrenal of normal female mice is associated with androgenic activity. It develops in the castrated male mouse in the absence of male hormone therapy, but testosterone injection prevents this development.

Females as well as males excrete androgens in the urine. Both sexes continue to excrete this material after gonadectomy, although in reduced amounts, particularly in males. Females with Addison's disease excrete little, if any, androgens in the urine (44, 19).

Patients with marked adrenal insufficiency tend to have aplasia of axillary and pubic hair. Males commonly have testicular atrophy.

Granting, then, that hypoandrogenism is commonly associated with adrenal insufficiency, the next point to establish is to what extent this deficiency is associated with the persistent weakness experienced by the individuals with this disease. The effects of testosterone are first considered since this substance has a much stronger androgenic effect than any other substance known (44). Whereas testosterone has not been shown to be derived from the adrenal, the latter apparently has the capacity to produce a testosterone-like substance, as evidenced by the clinical and laboratory data in classical cases of the adrenogenital syndrome. Furthermore, in males there is a possibility that the adrenal is concerned in the manufacture of testosterone precursors. Thus far, bulls' testicular tissue is the only material from which testosterone has been prepared in pure form.



Hoskins (24) found that castration diminished by about 60 per cent the voluntary activity of male rats. On the other hand, treatment with androgens increased the voluntary activity of castrated rats. Papanicolaou and Falk (50) found that testosterone caused muscle hypertrophy in guinea pigs. It has been known for a long time that eunuchs lack strength, energy and stamina. However, these handicaps can be largely removed with testosterone therapy. Testosterone propionate causes a depression in the urinary excretion of nitrogen, inorganic phosphorus, sulfate, sodium, potassium and chloride (28, 37, 40, 41, 43, 45). Creatine excretion, when substantial, may be depressed by this treatment (38, 41, 43). Methyl testosterone therapy provokes similar changes, but it is associated with an increased excretion of creatine (67).

The anabolic effects of testosterone have been utilized, with some success, in the treatment of Cushing's disease (1), Simmonds' disease (66, 68), and Addison's disease (39, 60). To a male and a female patient with Addison's disease, Kenyon and associates (39) administered 25 mg. of testosterone propionate daily for five days. They found that the response in the urinary constituents corresponded closely to that obtained in normal and hypogonad men and women. There was no alteration in the creatinine excretion in either case.

Talbot, Butler and MacLachlan (60) used testosterone therapy in an eight year old girl who had Addison's disease, moniliasis and idiopathic hypoparathyroidism. Methyl testosterone, in large doses (90 mg. daily), did not prevent the development of symptoms and signs of acute adrenal cortical insufficiency when desoxycorticosterone acetate was withdrawn. On the other hand, testosterone propionate in enormous doses, 50 mg. daily, "relieved the patient of all signs and symptoms of acute adrenal insufficiency after the discontinuation of desoxycorticosterone acetate therapy." With the testosterone treatment, used in conjunction with desoxycorticosterone and sodium chloride, there was a gain in body weight, a decrease in the

urinary excretion of nitrogen, potassium and sodium, and a marked fall in the serum potassium concentration.

Werner and West (66) reported that "striking subjective, objective, and laboratory changes followed the treatment with methyl testosterone of four patients with Simmonds' disease. Clinically, the patients demonstrated renewed vigor, sense of strength and libido, and redeveloped secondary sex characteristics." There was nitrogen retention associated with a persistent weight gain. Marked creatinuria developed after a latent period of several weeks and subsided in about the same length of time after stopping treatment.

We have followed the response to various types of androgen therapy in 11 patients with adrenal insufficiency (*supra vide*), six with Simmonds' disease and five with Addison's disease. Seven of these patients have been observed frequently for from two to three years, while the others have been followed for only a few months. Nine of the patients have been treated by the implantation of testosterone pellets, each patient receiving from 150 to 450 mg. Three of the patients have had replenishments of these pellets. Six subjects were treated with methyl testosterone for ten days or longer. One man has had several courses of methyl testosterone therapy, each lasting one to two months with intervals of one to several months between treatments. Six patients were treated with intramuscular injections of testosterone for one to five weeks; 25 mg. was given at one to two days intervals. Three patients were treated with androstanediol, and two with methyl androstanediol. The above therapy was given to some patients who were well regulated concerning the salt and water metabolism, and to others who were only partially regulated. Opportunities were afforded to observe the response to treatment while patients were working and also to note the results during infections.

In all cases the testosterone therapy resulted in increased strength, energy and sense of well-being. These changes occurred whether the therapy was given orally, intramuscularly or by the subcutaneous implantation of pellets. However, there was a difference in the

clinical response exhibited by the patients with Simmonds' disease as compared with those with Addison's disease. In the former the changes were apparent within a few days and progressed to the point where the improvement was of marked degree in each case. The response in the patients with Addison's disease was slower and in no case was it of marked degree; it tended to be only slight or moderate. It is not clear as to why this difference should exist. Each group of patients seemed to have about the same degree of adrenal insufficiency, clinically and as evidenced by the special laboratory studies. The treatment was similar in the groups, except that three of the patients with Addison's disease were not treated with desiccated thyroid.

The testosterone therapy did not have the same effect on the urinary constituents in each patient. However, it usually caused a decreased excretion of sodium, chloride, potassium, and nitrogen. Methyl testosterone caused no increase in the excretion of 17-ketosteroids whereas testosterone propionate caused an increase; these findings are in accord with those of previous observers (12, 19, 44, 60, 66). There was a slight increase in the excretion of creatinine following the methyl testosterone therapy, which was not continued long enough to observe the marked creatinuria reported by others (66, 67).

The clinical response to androstanediol was similar to that of methyl testosterone but of less degree. In neither of the two cases in which metabolic studies were conducted did the androstanediol cause nitrogen retention; indeed, there was an increased excretion. In one case there was a marked increase in the excretion of 17-ketosteroids, but no change in the other case. Others (12, 17) have reported an increase in the excretion of 17-ketosteroids following the administration of androstanediol, but no increase after the administration of methyl androstanediol (17). Only slight improvement resulted in the two patients treated with methyl androstanediol. In one, no changes resulted in the urinary constituents; in the other, there was a slight retention of potassium, nitrogen, creatinine

and creatine, but no change in the sodium, chloride or 17-ketosteroids.

With the continued observation of some of the above patients, one point becomes quite striking. After several weeks of therapy the water and electrolyte balance became well regulated, the patient gained weight and strength, and appeared capable of carrying on normal activity. However, within a short time after obtaining a job he would complain of the work being difficult and that he tired easily. Thus it appears that such individuals are lacking more in endurance than in "initial" strength. Although the muscle mass may be well developed, yet if there is a deficiency in the elements concerned in the repeated contractions of such muscles, fatigue and weakness will soon become apparent. In this connection the alterations in carbohydrate metabolism and the resulting effects on muscle performance may be considered.

In adrenalectomized animals or in patients with Addison's disease there is: (a) a marked decrease in liver glycogen (4, 48); (b) an increased carbohydrate utilization (13, 46, 63); (c) a decreased deamination in kidney tissue (32, 53), a decreased rate of formation of carbohydrate from amino acids (45); a normal rate of deamination (14, 45), in the liver and a normal rate of formation of carbohydrate from glutamic acid (45); (d) a decreased conversion in the liver of lactic acid (7), pyruvate or succinate (45, 63) to glycogen; a normal rate of conversion of succinic and pyruvic acid to carbohydrate in the kidney (53); (e) a decreased rate of oxidation of pyruvate and succinate by liver (64) and kidney (53) slices; and (f) a decreased muscle performance (23).

The alterations in carbohydrate metabolism may be corrected somewhat by therapy with salt, glucose or corticosterones. Adrenalectomized rats maintained in good health by the administration of sodium salts are said to show no abnormalities in the storage of carbohydrate (48). When, on the other hand, the adrenalectomized animal refuses food or when it is forced to fast, the liver glycogen declines to low levels, accompanied by less marked but significant declines in muscle glycogen and blood sugar values (47). Ingle

showed that muscular weakness develops shortly after adrenalectomy and is not corrected by injections of salt. Injections of glucose produced an improvement in the work-capacity approximately equivalent to that obtained by the injection of cortical hormone (30). A close parallelism has been shown (25-29, 36) to exist between the state of carbohydrate metabolism and the capacity of muscle to respond to stimulation.

Glucose that has been fed can be transformed into liver glycogen at essentially a normal rate in adrenalectomized animals (2, 35, 48); the hormones of the adrenal cortex are not essential for the deposition of glycogen (2, 48), but they exert an augmenting effect. The hormones which affect the deposition of glycogen and gluconeogenesis also markedly increase the capacity of muscle to respond to continued stimulation (36); these compounds have an atom of oxygen on C<sub>11</sub>.

In adrenalectomized animals the corticosterones cause: (a) an increased rate of storage of liver glycogen (4, 5, 6, 48), even in fasting animals; (b) an increase in urine nitrogen (48); (c) a decrease in carbohydrate oxidation (63); (d) a decrease in respiratory quotient (34, 63); (e) a decrease in glycogenolysis (11, 56); (f) an increase in the rate of conversion of keto acids to liver glycogen (45, 46); (g) an increase in blood sugar (5, 63); (h) an increase in the resistance to insulin (20, 21); and (i) an increase in the work-capacity of voluntary muscle (34).

In consideration of the problems involved in the patients with Simmonds' disease some of the alterations in carbohydrate metabolism in hypophysectomized animals are now presented. In hypophysectomized rats the administration of corticosterone and related compounds does not affect the glycogen in the muscle unless an extract of the anterior lobe of the pituitary gland is also given. There appears to be a synergism between the hormones of the adrenal cortex and those of the anterior lobe of the pituitary gland; either group alone is without effect on muscle glycogen (52). The depression of the oxidation of dextrose by corticosterone and related compounds

is likewise dependent on the secretion of the anterior lobe of the pituitary gland. The administration of corticosterone and related compounds to hypophysectomized rats without effect on the respiratory quotient unless an extract of the pituitary gland is also injected.

It is well known that the amount of glucose available in the body is important in muscular performance. In patients with Addison's disease the supply of glucose tends to be deficient; an adequate ingestion of salt and glucose aids in the storage of glucose, but corticosterone assures an adequate amount of glucose, provided that pituitary hormones are also available. In the treatment of the patients with adrenal insufficiency, a special effort was made to furnish an adequate supply of glucose by the frequent ingestion of food. Corticosterone was administered only a few days and only in four patients. The prolonged use of corticosterones in the doses necessary is not practical at the present time, but when corticosterones with an oxygen atom on C<sub>11</sub> are synthesized (36), this therapy will presumably produce very favorable results.

In the meantime the effects of stilbestrol on carbohydrate metabolism may be explored. Janes and Nelson (31) reported that diethylstilbestrol increased the liver glycogen of fasting rats and increased the excretion of nitrogen. The blood glucose and muscle glycogen were no different from those of the untreated normal animals. It is well known that estrogens, particularly diethylstilbestrol, cause great enlargement of the adrenal cortex which in turn is dependent on the stimulation of the anterior pituitary. Long (47) observed that the effects of diethylstilbestrol on carbohydrate and protein metabolism were due to its action through the pituitary on the adrenal cortex.

Stilbestrol dipalmitate was given for a few days to two patients with Addison's disease; each developed anorexia, nausea, and marked weakness. In neither case did the therapy increase the concentration of the blood glucose. Furthermore, insulin tolerance tests conducted before and after treatment in one case revealed no improvement.

## SUMMARY

Studies of the effects of various hormones and allied substances were made in 11 patients with adrenal insufficiency, six had Simmonds' disease and five had Addison's disease. The main objective was to produce a clinical improvement superior to that obtained with desoxycorticosterone acetate alone, particularly with regard to the patient's muscular strength. Testosterone propionate, testosterone pellets, methyl testosterone, androstanediol, and methyl androstanediol improved the strength, their effectiveness decreasing in the order named. In Addison's disease, the myosthenic effect was slight to moderate, but in Simmonds' disease it tended to be more pronounced. However, particularly in Addison's disease after the patient had worked for a few hours he noticed fatigue definitely more than normal. The deficiency in the corticosterones is regarded as the probable cause for this fatigue. Stilbestrol dipalmitate, given intramuscularly to two patients with Addison's disease, produced marked weakness, anorexia and nausea.

Metabolic studies were conducted in four patients with Addison's disease and in two with Simmonds' disease. There was a slight variability in the response. Testosterone propionate, for the most part, caused a retention of sodium, chloride, potassium, nitrogen, creatinine and creatinine, but an increase of 17-ketosteroids. Methyl testosterone caused a retention of sodium, potassium, nitrogen, and an increased excretion of creatinine, and no change in the 17-ketosteroid excretion. Androstanediol, given in large doses (80 mg daily) to one patient with Addison's disease, caused a slight retention of sodium and chloride, but an increased excretion of potassium, nitrogen and especially the 17-ketosteroids. Methyl androstanediol, given to two patients with Addison's disease, did not markedly affect the sodium, chloride, potassium, nitrogen, creatinine, creatinine or 17-ketosteroid excretion.

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# The Protein-Bound Plasma Iodine in Patients with Thyroid Disease<sup>1</sup>

## II. The Effect of Thiouracil

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SINCE the demonstration by the Mac-  
kenzie (7) that thiourea causes a depres-  
sion of thyroid activity in rats, the possi-  
bilities of this drug and its derivatives in the  
management of hyperthyroidism have re-  
ceived much attention. Astwood (1) first  
reported clinical improvement and a fall in  
the basal metabolic rate of patients treated  
with either thiourea or thiouracil. Thiourea,  
however, has been discarded by many workers  
in favor of the more active and less toxic  
thiouracil. Preliminary reports are now avail-  
able from several sources which indicate that,  
although thiouracil has the ability to cause  
varied and severe reactions, its administra-  
tion to hyperthyroid patients is followed al-  
most invariably by considerable clinical im-  
provement and decrease in the basal meta-  
bolic rate (1, 2, 4, 6, 8-10). Recently it has  
been shown that this drug also reverses the  
biochemical alterations of the thyrotoxic pa-  
tient in a manner similar to the reversal pro-  
duced by lugolization or thyroidectomy (9).

The mechanism of the action of thiouracil  
has not been clearly established. Since it does  
not abolish the activity of exogenous thy-  
roxin (3) it is believed that the drug acts by  
inhibiting the synthesis of thyroxin in the  
thyroid gland. If this is the case, the protein-

bound plasma iodine (hormonal iodine) may  
be expected to decrease parallel to the fall in  
metabolism.

### MATERIALS AND METHODS

The plasma concentration of protein-bound  
iodine and the basal heat production were de-  
termined as described previously (5). These  
were performed on patients with hyperthy-  
roidism who were being treated with thio-  
uracil. The present report embraces 18 conse-  
cutive cases of toxic diffuse goiter in which  
the drug was used for periods ranging from  
eight days to four months. In thirteen cases,  
thiouracil was prescribed for from two to four  
months in order to determine its value in the  
medical management of hyperthyroidism; in  
four cases, it was employed only preopera-  
tively; in one, the drug was withdrawn at the  
end of the third week because of neutropenia.

The thiouracil<sup>3</sup> in all cases was adminis-  
tered orally, usually 100 mg. tablets being  
given singly at intervals throughout the day.  
For most patients 100 mg. every six hours  
(400 mg. per day) was an adequate initial  
dose, although occasionally 100 mg. every  
four hours (600 mg. per day) was given. In  
five to eight days, this initial dose was re-  
duced to 100 mg. every eight hours (300 mg.

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tion.

<sup>2</sup> Research Assistant in Medicine.

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Stanton Hardy of the Lederle Laboratories for a generous  
supply of 100 mg. tablets of 2-thiouracil ("Deracil").

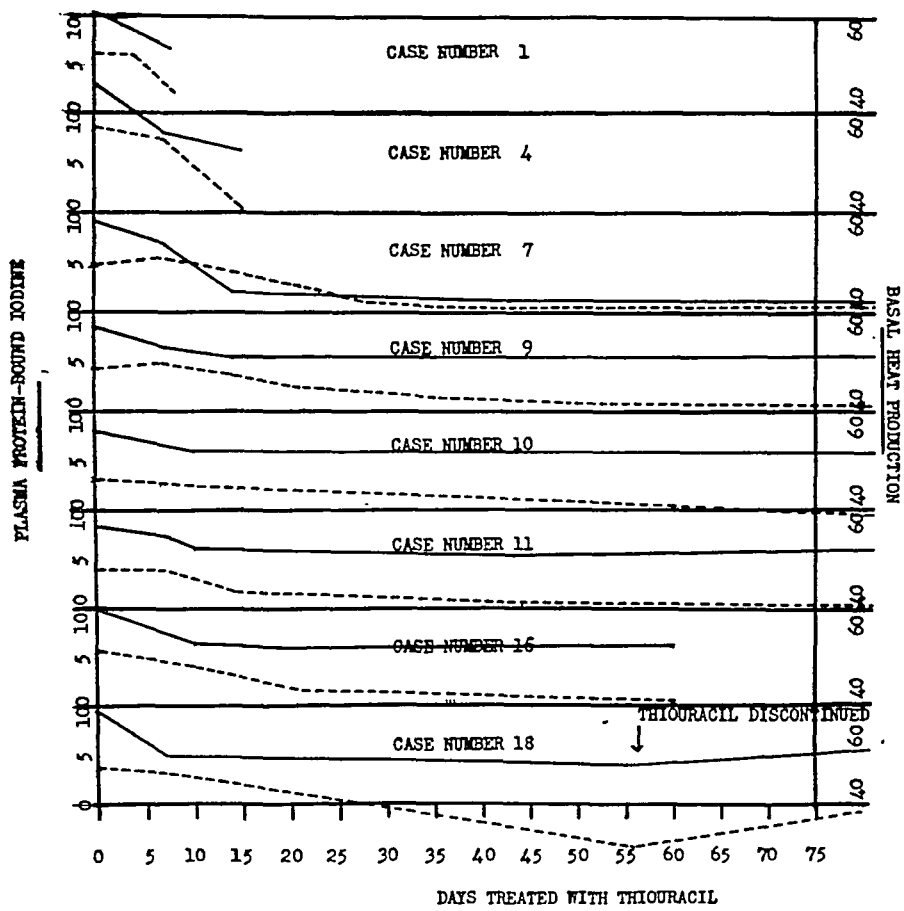


FIG. 1. The laboratory course of eight patients treated with thiouracil is illustrated in the above figure. The solid line represents the protein-bound plasma iodine in microgram per 100 cc. of plasma and the dotted line shows the basal heat production in calories per square meter per hour.

TABLE I. THE EFFECTS OF THIOURACIL ON THE PROTEIN-BOUND IODINE, BASAL HEAT PRODUCTION AND PLASMA CHOLESTEROL IN 18 PATIENTS WITH TOXIC DIFFUSE GOITER

Case Number	Initial					Thiouracil Treatment			Final					Remarks
	Plasma iodine gamma %	Basal heat production cal./sq.M./hr		B.M.R. %	Plasma cholesterol mg. %	Initial dose mg./day	Days treated	Maintenance dose mg./day	Plasma iodine gamma %	Basal heat production cal./sq.M./hr		B.M.R. %	Plasma cholesterol mg. %	
		calc.	det.							calc.	det.			
1	10.5	52.7	52.5	+50	168	600	8	—	7.0	42.5	41.5	+18	184	Thyroidectomy on 9th day. Thyroidectomy on 10th day. Thyroidectomy on 13th day. Thyroidectomy on 11th day. Lugol's solution for 2 weeks before thiouracil failed to change B.M.R.. Thiouracil discontinued on 24th day on account of WBC 4050 (P 31%) on normal blood count.
2	7.4	44.7	45.4	+22	177	400	10	—	6.0	39.9	40.0	0	236	
3	17.7	64.5	65.3	+62	90	400	12	—	7.0	42.5	43.1	+9	198	
4	12.8	57.0	56.1	+40	110	600	10	—	6.1	40.3	42.0	+5	190	
5	7.2	44.0	41.6	+16	160	600	24	—	5.3	37.9	37.0	+3	254	Persistent tachycardia of 120/min. with palpitation and exertion. Had lucid heart disease. Anxiety; still complains of palpitation and nervousness. This patient had a recurrence of symptoms of thyrotoxicosis on 50 mg. thiouracil but was well on 100 mg. thiouracil. Early symptoms of hypothyroidism became evident.
6	11.6	55.6	55.4	+29	134	600	118	200	6.8	42.7	42.5	-1	284	
7	9.1	49.3	49.9	+29	100	600	124	200	6.0	39.9	40.0	+4	202	
8	14.0	59.2	62.5	+63	120	600	122	200	6.7	42.5	42.2	+10	190	
9	8.4	47.5	48.5	+35	200	400	91	200	5.7	38.8	40.7	+14	192	
10	8.0	46.4	46.4	+25	215	400	96	200	5.7	38.8	38.0	+2	198	
11	8.3	47.7	48.1	+28	142	400	88	200	6.1	40.3	40.0	+6	156	
12	7.8	45.8	45.3	+26	170	400	80	100	4.3	32.4	33.6	-6	300	
13	9.0	49.2	54.1	+41	164	400	73	100	5.3	37.9	41.8	+9	326	
14	6.5	41.8	40.0	+21	146	400	69	100	4.9	35.3	35.1	+6	268	
15	11.0	53.8	53.5	+63	96	400	70	200	5.0	35.8	34.9	+8	200	
16	10.0	51.5	51.5	+29	110	400	60	100	6.1	40.3	40.5	+1	288	
17	8.4	47.5	46.9	+22	—	400	60	100	5.6	38.3	38.5	0	—	
18	9.1	49.3	47.5	+22	188	400	56	100	4.0	30.7	30.4	-22	400	

per day) and within two weeks this was again decreased to 50 or 100 mg. every 12 hours (100-200 mg. per day). Urinalyses, blood counts and basal metabolisms were done at weekly intervals. Vitamin B complex, Lederle (3 capsules a day), and ascorbic acid (200 mg. a day) were prescribed simultaneously. Cases 7 through 18 also received 250 mits of "folic acid" (grass juice concentrate)<sup>4</sup> per day.

When thiouracil was used preoperatively, thyroidectomy was performed 8 to 12 days after instituting treatment with the drug. On this regime, the basal metabolism was at or near normal levels at the time of operation. No severe technical difficulties (J.W.H.) were encountered during surgery.

#### RESULTS AND DISCUSSION

The results are summarized in the accompanying table and some representative cases are graphed in the figure. Within 4 to 7 days after the beginning of treatment, the protein-bound plasma iodine usually had begun to drop toward normal levels. In most cases, the iodine had reached the normal range within two weeks. The basal heat production fell more slowly, seldom declining within a week after the institution of treatment. However, by the end of the second week the basal heat production had also decreased to approximately normal levels. The basal heat production could be calculated from the plasma protein-bound iodine concentration using the equation  $BHP = 52.3 \log (I) - 0.8$  calories per square meter per hour, previously shown to be accurate for patients with thyroid disease and after lugolization or thyroidectomy (5). This calculation yielded accurate results both before treatment and after the thiouracil had caused the blood iodine and the basal heat production to reach a steady state. The mathematical correlation, however, was inaccurate in the period during which the metabolic rate and the iodine concentration were declining. These results agree in a general way with those obtained by Williams and Bissell (10) who found a decline

in the plasma iodine concentration of thiouracil treated patients. These workers, however, made no attempt to correlate the plasma iodine with the basal metabolic rate.

These results are entirely compatible with the assumption that thiouracil interferes with the synthesis of thyroxine. In this case, one would expect exactly what was found: the first detectable effect of the drug is a fall in the circulating thyroid hormone as measured by the protein-bound plasma iodine. Later, the basal heat production also declines as the thyroid hormone available to the body decreases.

It should be mentioned that no patient in this series showed any change in the size of the thyroid gland or in the degree of exophthalmos following thiouracil administration. As yet, thiouracil has not been discontinued in any of the long-term treated patients in order to see if persistent remission of the hyperthyroidism could be obtained as recently described by Astwood (2).

#### SUMMARY

Thiouracil (when administered to 18 patients with hyperthyroidism) caused a reduction in the basal heat production and in the protein-bound iodine of the plasma.

After these changes have been produced, the relationship previously demonstrated (5) between plasma iodine concentration and basal heat production was found to be entirely valid.

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<sup>4</sup> This material was furnished through the courtesy of C. Balfour Associates, Englewood, N. J.



# Premature Sexual Precocity in a Young Girl

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PREMATURE sexual precocity is not rare. In the case reported here, daily gonadotropic, estrogenic, androgenic (17-ketosteroids) and progestin metabolic products (sodium pregnanediol complex) assays were made almost every day for 50 days. This child apparently was endocrinologically a normal adult female, but in age a child.

## CASE FINDINGS

*R.J.*, a girl 4 years and 11 months of age, was brought to the author's office because of precocious menstruation and abnormally rapid growth. She was born February 21, 1935, as shown by the birth certificate; delivery was normal. She weighed  $9\frac{3}{4}$  pounds at birth and 17 pounds at two months.

The father of the patient was 32 years old, weighed 128 pounds and was 5 feet and 8 inches tall. The mother was 28 years old, weighed 173 pounds and was 5 feet and 5 inches tall. The mother's menstrual periods began at the age of 12 years. The patient had one sister, 10 years old, apparently normal.

The patient's weight was 72 pounds and her height was 4 feet and  $5\frac{1}{2}$  inches. The pulse rate was 104; heart sounds were normal. The respiration rate was 20 per minute; there were no râles. The circumference of the head at the brow was 22 inches; chest, 27.7 inches; abdomen at umbilicus, 26.1 inches; hip at trochanter, 20.1 inches; span, 57.6 inches; height, trochanter to floor, 30.1 inches; trochanter to top of head, 33.5 inches. Pelvic measurements were: anterior superior spine, 19.5 cm.; intercrestal, 23 cm.; external oblique (right and left), 19 cm.; transverse outlet, 8 cm.

The hair was short, and was dark brown color. The eyes were normal. All of the deciduous teeth were present. The skull was rather large, the neck normal. The body was well developed generally. The breasts were large, measuring 6 cm. in diameter, and the fatty-glandular tissue was 3 to 4 cm. deep. The nipples were well developed, pink and inverted. The abdomen was normal except that its skin was somewhat scaly and showed some old scars from a skin infection (see Fig. 1).

The external genitalia showed a scant growth of pubic hair. There was no axillary hair. The vaginal orifice admitted one finger with difficulty. There was no unusual development of the labia. The mucosa was similar to that of the normal adult (see fig. 2).

Rectal examination revealed an apparently normal cervix and uterus. The pH of the cervical secretion was 7.4 and of the vaginal secretion, 4.0. There was a questionable mass felt in the right adnexa, but none in the left. There was no menstrual flow at the time of the examination.

The mother stated that the baby's breasts were unusually large at birth. She noticed that the baby at two years of age was much larger than other children and also larger than her first child at this age. She seemed to be precocious mentally, although she liked to play with dolls and her attitude toward both boys and girls was the same as that of other children.

In the fall of 1938, when the child was four years old, the mother noticed that she had vaginal bleeding. This occurred again after an interval of 30 days, lasting only one day.

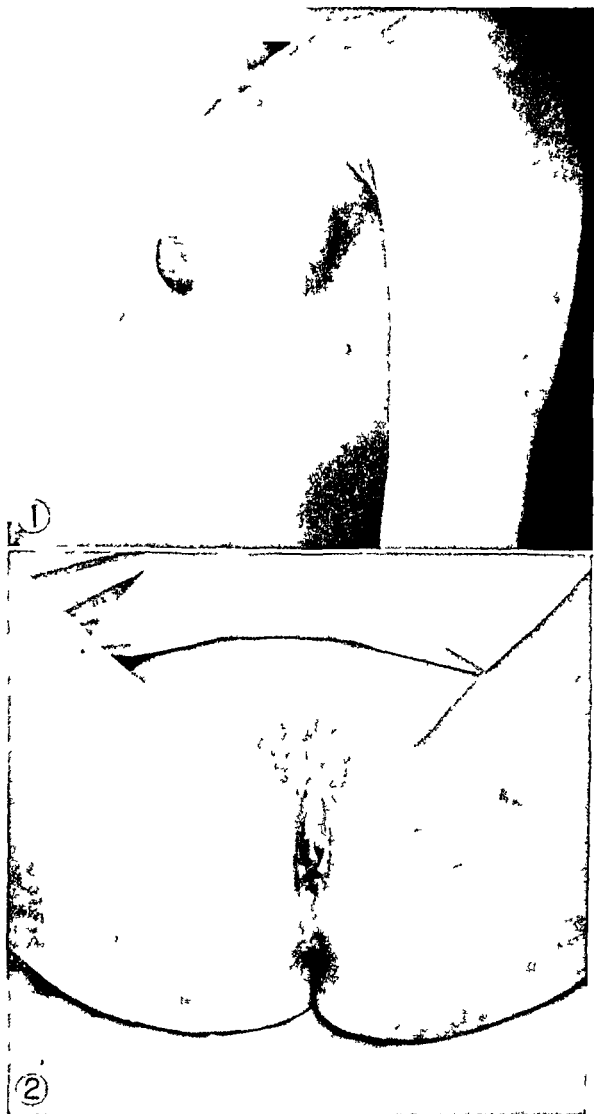


FIG 1 The torso of patient *R J*

FIG 2 The perineum of patient *R J*

On January 11, 1940, the patient began to have a profuse flow which lasted six days and was not accompanied by pain.

She was hospitalized on February 5, 1940. Examination showed the cardio-vascular and gastro-intestinal systems to be normal. The breasts were large and the body generally was well developed.

The findings of psychological tests made on February 9, 1940, were: chronological age, 5 years; Stanford-Binet mental age, 5 years; Stanford-Binet intelligence quotient, 100; Goodenough mental age, 5 years 9 months; Goodenough intelligence quotient, 115.

These findings yield a tentative rating of average intelligence. There is some suggestion that, with complete coöperation, the patient might have been able to rate some points higher. She succeeded at the six year level in some tests, such as the vocabulary test. The examiner estimated that a maximal rating on the patient, as to general intelligence, would be represented by an I.Q. of 109, indicating a classification of average intelligence. The quality of her responses does not suggest superior ability.

### PROGRESS

The child remained in the pediatric ward for 83 days. Her only illness was an impetigo with a slight elevation of temperature.

A twenty-four hour urine specimen was collected, and pituitary and estrogenic hormones were determined by the author and also by Dr. W. K. Cuyler of Duke Hospital, Durham, N. C.

An exploratory laparotomy was performed by the author on March 26, 1940. Upon opening the abdomen it was seen that the ovaries, tubes, and uterus were adult in size and appearance. The uterus measured approximately 5.5 by 3 cm. and was pearly white in color. Both ovaries were sectioned lengthwise and throughout the stroma were many small yellowish bodies. Eight of these were removed. Also, a section of about  $\frac{1}{8}$  of each ovary was removed for further study. A biopsy of the left breast was done by Dr. R. C. Patrick. She recovered from the operation uneventfully.

The child began to bleed exactly 48 hours after being operated upon and bled for 33 hours. Then, on June 8 she bled again for 1 hours. This was more of a spotting than regular flow. During this flow the pH of the vaginal secretion was 7.3, and 12 hours after the flow stopped it was 4.5. The pH of the vaginal fluid was determined almost every day, and it varied from pH 3.8 to 4.6.

She was seen in the author's office at intervals of from six weeks to six months after dismissal from the hospital. The last visit was April 19, 1945.

### ASSAYS

Urine specimens were received daily at Duke University from February 16, 1940 to April 5, 1940.

I. *Sodium Pregnanediol Complex* (progestin metabolic product): The total daily excretion before operation was 122 mg. The melting point was 240 degrees centigrade. The average total daily excretion after operation was 19 mg. (no melting point; 46 determinations).

II. *17-Ketosteroids* (androgenic metabolic products): The daily average value of 17 ketosteroids before operation was 29 I.U. and the daily average after operation was 1 I.U. (49 determinations).

III. *Urinary Estrogenic and Gonadotropic Values (per 24 hour period):*

Date	Estrogen Values Rat Units	Gonadotropic Values Rat Units
2-16-40	54	
2-17-40	46	
2-18-40		7.5
2-20-40	30	
2-21-40	30	
2-22-40		7.5
3- 3-40	38	
3- 4-40	12	
3-13-40	11	
3-14-40	15	5.0
3-24-40		
3-25-40	35	
3-26-40	49	
3-37-40	32	
3-28-40	14	
4- 2-40	5	
4- 3-40	9	5.0
4- 4-40		

In our own endocrine laboratory on February 6, 1940, the estrogen assay showed 24 rat units per 24 hours, and was negative for

pituitary gonadotropin. On February 9, 1940, the assay showed 20 rat units of estrogens, and again was negative for pituitary gonadotropin. Dr. A. E. Rakoff of Philadelphia found 3 to 6 mouse units of estrogen per 100 cc. of blood. The extraction of estrogen was performed in our laboratory by the method of Kurzrok (1).

#### ROENTGENOGRAPHIC STUDIES

Roentgenograms of the skull showed it to be characteristic of a child of about 12 years of age. The thymus was not enlarged; the bones of the hands and forearm had the appearance of those of a child about 10 years of age; the epiphyses of the knees and ankles showed the amount of union expected in a child of about 15 years of age; the teeth were those of a child of four years and eleven months; the skioidan technique revealed the uterus to be larger than normal. The tubes were patent. In the intravenous urogram the kidneys appeared normal in size, shape and position.

#### OTHER LABORATORY TESTS

The sedimentation rate was 18 mm. in one hour; the erythrocyte count was normal; the serum chloride, sugar, total non-protein nitrogen, creatinin, urea nitrogen, uric acid, and the glucose tolerance were all normal. The blood cholesterol was normal. The urine was normal.

#### SURGICAL PATHOLOGY

Endometrial biopsies were taken on February 7, 1940, September 6, 1940 and December 16, 1940. Two showed a normal proliferative stage of the endometrium and one was suggestive of secretory endometrium. A vaginal biopsy showed an adult type of mucosa.

*Specimen Obtained at Operation, March 26, 1940.* "Microscopic: (1) Sections of endometrium show small glands, the epithelium of which in a few places presents early proliferative changes. A few of the epithelial cells show vacuoles at the base and the nucleus is pushed toward the center of the gland. The stroma is dense and normal throughout.

(2) Sections of right ovary show numerous immature nonripening ova lying in the usual ovarian fibromuscular tissue. I can find no evidence of ripening follicles and no corpora hemorrhagica or corpora lutea. Iron stains fail to reveal any evidence of pigment such as should be present. (3) Sections from the left ovary are similar to those on the right. (4) Section of left breast present small glands, a few of which are dilated and are lined by flattened glandular epithelium. The glands are lying in a heavy connective tissue matrix similar to that of the young breast before puberty, yet the glands are of a more adult type. There is no evidence of proliferation of the glandular epithelium such as a secretion of the breast would give, but I feel that there is sufficient evidence here to indicate that the breast is abnormal for a child of this age and is much more mature than one would expect. (5) Section of a small nodule found in the left broad ligament shows a thin capsule within which are multiple large cuboidal cells with vacuolated cytoplasm and large central nuclei which are deeply stained and round. These cells resemble the cortical cells of the adrenal gland and are evidently an adrenal rest. (6) Section of a cyst taken from the left Fallopian tube shows the lining to be composed of epithelioid cells, but in the opinion of the writer these are endothelial cells taking on the process of secretion. The wall is loose connective tissue and I believe this can be classified as a peritoneal inclusion cyst.

"*Diagnosis:* endometrium, partly in resting, partly in very early proliferative stage; normal ovary; adrenal rest; peritoneal inclusion cyst."

#### COMMENTS

A case of premature sexual precocity in a girl age 4 years and 11 months is presented with the data of numerous hormonal assays performed upon her urine and blood. There were 17 assays of estrogenic hormone, 7 of gonadotropin, 46 of the 17-ketosteroids (androgenic metabolic products). The values obtained were approximately those found in a normal adult woman.

The appearance of the vaginal mucosa and

the values of vaginal hydrogen ion concentration were those of an adult woman.

The ovaries, Fallopian tubes, uterus, cervix and vagina were also those of a normal adult female.

Both ovaries showed throughout many yellow bodies (believed to be adrenal rests) and similar bodies were scattered over the anterior and posterior peritoneal surfaces of the uterus and both broad ligaments. The pelvic peritoneum was studded here and there with these minute yellow raised areas. This case may represent an example of adrenal rests causing feminization instead of the usual masculinization, as described by Novak. Both Dr. Erickson of the Department of Pathology of Duke University and Dr. Donald Henderson of the Department of Pathology of Jefferson Davis Hospital diagnosed these yellow bodies as *adrenal rests*.

#### SUMMARY

The case is reported of a girl, aged four years and eleven months, who had approximately the genital development of an adult woman. The personality and intelligence were appropriate to the chronological age.

The urinary estrogen ranged between 5 and 54 rat units per 24 hours. Gonadotropin values varied from 5 to 7.5 rat units.

At operation numerous cell agglomerations were found within the ovary and studding the peritoneum. These upon microscopic study were diagnosed as adrenal rests.

The case apparently adds one more to the list of published instances of feminization from functioning adrenal rests in ovaries.

#### ACKNOWLEDGMENTS

The writer wishes to express appreciation to Dr. J. E. Hodges and Dr. Tom Kennerly for their kind assistance in this case. Thanks are also due Dr. E. C. Hamblen, Mr. Cuyler, Miss Baptist and Mrs. Astley of Duke University for determining the titers on the 50 consecutive urines. The work of Dr. Donald Henderson, pathologist at the Jefferson Davis Hospital has been extremely helpful. The writer is greatly indebted to Mrs. Susie Kemp, in charge of the pediatric department, and to all the excellent nurses and internes who helped with this case. Of especial helpfulness were the pathological reports submitted by Dr. Erickson, Department of Pathology, Duke University.

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# EDITORIALS

## IMPROVED FORMS OF INSULIN

THE GREAT facts forever foremost in the minds of those who treat patients with diabetes are that insulin is easily available almost everywhere and that with its proper use death from diabetes need not occur and normal health and vigor are possible. The majority of students of the disease are agreed that the more nearly normal the blood glucose values are throughout the day, the greater are the chances to keep the diabetic patient in an optimal state of well-being. Regular insulin caused wide fluctuations in blood glucose levels and required multiple injections. Therefore, various slowly acting types of insulin were tried, and protamine-zinc insulin has emerged as the most widely used form for maintenance therapy. It was hoped that a single injection daily of protamine-zinc insulin would suffice to establish good control in the great majority of cases.

This hope has not been realized. Only the milder cases (usually those requiring forty units or less daily) can be well regulated with protamine-zinc insulin alone. The present market form of protamine-zinc insulin is entirely a precipitate which is slowly absorbed over a period of twenty-four hours or more. In mild cases, in which the rise in blood sugar after meals is not great, such an insulin may prevent hyperglycemia during the day as well as during the night. In severe cases, however, it is usually not possible to give enough protamine-zinc insulin to control the blood sugar rise after food intake without causing nocturnal hypoglycemia. Such hypoglycemia does not occur "because protamine-zinc insulin acts strongest at night," (an over-worked and inaccurate cliché), but because of the failure to take food at regular intervals during the night. If the patient ate regularly every four hours day and night protamine-zinc insulin, because of its slow, constant activity, should prove ideal.

For practical purposes a compromise or combined form of insulin therapy is often very satisfactory: two separate injections are given each morning, one of protamine zinc insulin (P.Z.I.) and one of regular insulin (R.I.). Usually the amount of P.Z.I. needed is about three times as

large as the dose of R.I. required and the patients receive P.Z.I. forty-five units and R.I. fifteen units, or P.Z.I. sixty units and R.I. twenty units, etc. Although this is probably the best plan which is possible with the present market forms of insulin for patients with severe diabetes, it is far from ideal. Two injections daily are necessary, and patients often become confused with the two different types of insulin and two different sized doses.

Efforts to devise an insulin which, with a single injection daily, would establish good regulation in severe as well as mild cases have taken several directions: (1) proteins other than protamine, such as globin and histone, have been combined with insulin; (2) protamine-zinc insulin has been modified by varying its protamine and zinc content, and by changing the pH.

Histone-zinc insulin and globin-zinc insulin have been rather thoroughly studied. Neither of these modifications has given both the rapid effect and the prolonged activity desired. Modifications of protamine-zinc insulin containing only a half or a third as much protamine as market protamine-zinc insulin have given the most encouraging results. Two types of insulin with such lower protamine content have been suggested: (1) a biphasic insulin containing about twenty-five per cent of the hormone in quickly absorbable form, and seventy-five per cent in precipitated slowly absorbable form—this has been designated M.P.Z. insulin by MacBryde (4, 5); and (2) a monophasic insulin in which all of the hormone is precipitated. The precipitate, however, is saturated with insulin and there is no excess protamine, so that the hormone is more quickly released than from standard P.Z.I., which contains a large excess of unsaturated protamine. This is essentially the product obtained by mixing crystalline insulin with P.Z.I. in the proportion of 2:1, as suggested by Colwell (1).

There have been several comparative clinical studies of the suggested new insulins. Peck (6) obtained good results both with the modified protamine-zinc (M.P.Z.) insulin and with a 2:1

crystalline-P.Z.I. mixture, the comparative figures being somewhat better with the former. Del Fierro and Sevringhaus (2) established good control in fifteen of seventeen cases with M.P.Z. insulin and found it superior to P.Z.I., globin-zinc insulin or mixtures. MacBryde and Reiss (3) compared M.P.Z. insulin with the 2:1 mixture in a series of ten severe cases and reported better twenty-four hour blood sugar curves in every case with the M.P.Z. insulin; the control with M.P.Z. insulin excelled that obtainable with globin-zinc insulin in 17 of 20 cases.

At the present time evidence seems to indicate that protamine-zinc insulin, modified by a considerable reduction in its protamine content, will in one of its forms prove to be the preferable insulin for maintenance therapy. Whether the type which seems to give the best results clinically (M.P.Z. insulin, containing both rapidly absorbable and slowly absorbable components) will prove sufficiently stable remains to be demonstrated. It would seem logical that a biphasic insulin could best control both the hyperglycemia following meals and the constant

glycogenolysis demanding a small but steady supply of insulin every hour of the day and night.

C. M. MACB.

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## ON MENSTRUATION

FROM the point of view of pathology, menstruation is a disease. No other "normal" function, with the presumed exception of labor and delivery, involves edema, leucocytic infiltration, ischemia from arteriolar spasm, capillary and arterial rupture and sloughing of tissue. The menstrual discharge resembles the blood found after death from overwhelming shock or pregnancy toxemia. From the point of view of pathologic physiology, no other "normal" process except the termination of pregnancy involves such rapid and large shifts in water metabolism, in creatinine excretion and in serum diastase and changes in systemic vascular physiology slightly suggestive of shock. No other "normal" episode except the onset of lactation is accompanied by such a rapid and often striking, though fortunately usually short-lived, disturbance in personality. Furthermore, the skin eruptions, sore breasts, headaches, backaches, thigh-aches, cramps, nasal congestion, dizziness, chilly sensations, abdominal discomfort and change in activity of bowel and bladder all bespeak a pathological phenomenon.

The Greeks were indeed correct in associating hysteria with the uterus, for neither the menstrual molimina nor such marked evidence of disturbed physiology have been observed in its absence. Though objective information is scant, the subjective molimina are also mild or absent in patients with estrogen-induced flowing, cyclic bleeding from a proliferated endometrium or functional flowing from a proliferated endometrium.

According to available information, true post-ovulatory menstruation is a widespread shedding of the endometrium; whereas bleeding from an estrogen-stimulated, proliferative endometrium is focal, there being far less breakdown of tissue. The debris of secretory endometrium, separated from the menstrual discharge, has been found extremely toxic (1). Late secretory, premenstrual endometrium fresh from the operating room, ground and injected in saline suspension into immature rats has been found toxic. (2). Proliferative endometrium, even with hyperplasia, is not toxic. Thus it appears that the regression of a secretory endometrium is accompanied by a me-

politic change which yields a toxin. This toxin is the likely final cause of menstruation through vascular corrosion. It is suggested that menstruation and shock have much in common, both locally and systemically. Spontaneous debridement relieves the menstrual toxemia just as surgical debridement ameliorates that of traumatic shock.

The above considerations indicate that, in addition to the hormonal component involved in the menstrual phenomenon, there is another component, related to the change in endometrial metabolism. What other purpose can this other component serve besides relieving the uterus of a tissue unrequited by the receipt of a fertilized ovum, since there are systemic as well as local reactions to it?

The urinary FSH is increased just before or at the start of menstruation. The premenstrual engorgement of the breasts may be interpreted as reflecting pituitary lactogenic activity. The drop in serum diastase at this time can be thought of as evidence of increased adrenocortical activity, thus intimating a rise in the output of adrenocorticotrophic hormone. The premenstrual retention of water invites the idea that stimulation of the posterior lobe has occurred.

It seems hardly possible that these suggested evidences of menstrual hypophyseal activity could be due to nothing more than regression of the corpus luteum. The very fact that nor-

mal corpora lutea have been observed in patients whose wombs have been removed and in whom molimina are absent confirms this conclusion. Furthermore, any cyclic pituitary-ovarian interaction in these patients has not yet been shown. Actually, patients with a tiny amount of endometrium left after supracervical hysterectomy are likely to have "aperiodic" staining.

Can it be that the toxemia of menstruation, resulting from the regression and disintegration of secretory endometrium, is in primates a necessary supplement to regression of the corpus luteum for adequate cyclic hypophyseal stimulation? If, so, the induction of cyclic post-ovulatory-like bleeding is to be recommended for patients with functional disturbances, *viz.*, amenorrhea, abnormal bleeding and irregular cycles, in which "normal" (*sic*) hypophyseal stimulation is desirable.

On the basis of the above considerations, it would seem desirable, even urgent, to have available ampules containing 10, 15, 20 and 25 milligrams of progesterone, at a cost that would not unduly restrict their use.

GEORGE V. SMITH

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# ASSOCIATION NOTICE

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The Association for the Study of Internal Secretions has just announced that the award furnished by E. R. Squibb and Sons has been given to Dr. E. C. Kendall and that the award furnished by Ciba Pharmaceutical Products Inc. has been given to Dr. Jane Anne Russell (Mrs. A. E. Wilhelmi).

The Squibb Award to Dr. Kendall, was based on his fundamental contributions to endocrinology, in particular the isolation of thyroxine from the thyroid gland and his recent observations on the fractionation and functions of active principles of the adrenal cortex. Dr. Kendall is professor of biochemistry in the Graduate School, Mayo Foundation, University of Minnesota. He received the degree of Bachelor of Science from Columbia University in 1908 and the degree of Doctor of Philosophy from the same institution in 1910. He then held various fellowships until he became affiliated with the Mayo Clinic in 1914. He was given the

honorary degree of Doctor of Science by the University of Cincinnati in 1923, and was president of the Association for the Study of Internal Secretions in 1930.

The Ciba Award was made to Dr. Russell because of her fundamental observations on the rôle of the anterior pituitary, adrenal and thyroid glands in the absorption and utilization of sugars and starches. Dr. Russell is an instructor in physiological chemistry at Yale University School of Medicine. She received the degree of Bachelor of Arts from the University of California in 1932 and the degree of Doctor of Philosophy from the same institution in 1937. She has held various fellowships, the most important of which are the Porter Fellowship of the American Physiological Society, a National Research Council fellowship in medicine and the Sterling Fellowship in the Department of Physiological Chemistry at Yale University.



# CURRENT ENDOCRINE LITERATURE

Editor, D. A. McGINTY. Collaborators: F. A. DE LA BALZE, ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, INA FORBES, E. C. HAMBLIN, CHARLES W. HOOKER, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, R. REFORZO-MEMBRIVES, A. E. MEYER, DORIS PHELPS, E. C. REIFENSTEIN, JR., RUTH ST. JOHN, HAROLD WOOSTER, RD J. ZANARTU.

## ENDOCRINE GENERAL

RAU TRIANA, JUAN, D. ARGUELLES CASSALS, O. ROMERO JORDAN AND A. BULLE MERRY. Xanthoma diabeticorum and gigantism-acromegalia syndrome. *Vida nueva* 53, 274. 1944.

Report of a case of xanthoma diabeticorum a white girl, fifteen years of age, presenting so manifestations of diabetes mellitus and a gigantism-acromegalia syndrome. The xanthoma was considered a secondary manifestation of the hyperlipemia, which in turn is a complication of diabetes.

The case is interesting for the following reasons: Xanthoma diabeticorum is a rare disease (31 cases in the literature, in 1941). Xanthoma diabeticorum is rare in women. For each female there are seven male cases. The association of the gigantism-acromegalia syndrome gives great importance to the pituitary factor in the pathogenesis of the disease.

The evolution of the case (the skin lesions were cured with a fat-free diet and injections of insulin) is characteristic of the disease and serves to confirm the diagnosis in an evident manner.—*Courtesy Diabetes Abstracts.*

ADDOW, A., J. M. WATKINSON, E. PATERSON, AND P. C. KOLLER

Influence of synthetic estrogens upon advanced malignant disease. *Brit. Med. J.* 2: 393. Sept. 23, 1944.

Seventy-three cases of advanced cancer received treatment with the synthetic estrogens triphenylchloroethylene, triphenylmethylethylene, or stilbestrol. Of 22 cases of late malignant disease of the breast treated with triphenylchloroethylene (usually in doses of 3 to 6 gm. per day over a period of several months), 10 showed a significant although temporary retardation, or even partial regression, of the tumor. No evidence was obtained to suggest

that the drug will prevent the development of metastases. The initial effect of treatment in these cases passed off comparatively rapidly, and only one has shown prolonged arrest, the ultimate course of the disease being in no way altered in the remainder. The degree of retardation was less than could be expected from local palliative x-irradiation. Of 30 cases of advanced malignant disease other than cancer of the breast (including carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis with reticuloendothelial growths and leukemia), and similarly treated with triphenylmethylethylene, only 2 (carcinoma of the bladder, carcinoma of the prostate) showed undoubted partial regression of the tumor. Of 14 cases of carcinoma of the breast treated with stilbestrol (average of 300–600 mg. by intramuscular injection or by mouth over a period of several months), 5 showed alterations in the growth and behavior of the tumor similar in nature to those produced by triphenylchloroethylene. Serial biopsies in a few cases with a marked clinical response showed histological alterations (diminution of mitosis rate, variations of staining behavior, and necrotic changes) of a type not resembling the changes following x-irradiation. The secondary signs of drug action included nausea, pigmentation of the mammary areola, mastitis in the male, uterine bleeding, and edema of the lower extremities. One or more of such changes occurred with special frequency in cases showing some degree of tumor regression. Several of these cases also manifested improved appetite, gain in weight, and diminution of pain.—R.B.G.

HERTIG, A. T., AND R. G. LIVINGSTONE

Spontaneous, threatened and habitual abortion: their pathogenesis and treatment. *New Eng. Med. J.* 230: 797. June 29, 1944.

Threatened abortion occurs in at least 16 per cent of all pregnancies. Spontaneous abortion

occurs in approximately 10 per cent of all pregnancies. Approximately 40 per cent of threatened abortions do not abort regardless of the treatment employed. Approximately 60 per cent of threatened abortions abort if untreated. On the basis of a series of 1000 cases examined embryologically and pathologically, approximately one-third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician. In view of the three preceding conclusions, approximately 60 per cent of threatened abortions under adequate treatment may fail to abort. Threatened abortion should be treated by some potent corpus luteum preparation or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C and K and thyroid, in conjunction with a program of so-called "nutritional adequacy." Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to or coincident with conception.—*R.B.G.*

#### JACOBSON, P.

The psycho-endocrine origin and therapy of recurrent spontaneous hemorrhage. *Virginia Med. Monthly* 72: 73. 1945.

Estrogen by injection produced hemostasis in 49 patients with various types of hemorrhage, as epistaxis, from gastric ulcer, tonsillar fossae, or in idiopathic hematuria. Doses of 2000 to 5000 units were administered to children and adolescents, and 10,000 units to adults. Epistaxis occurred in from one-half to three hours. The author believes that patients with spontaneous hemorrhage suffer from emotional hypertension, and estrogen may serve to affect the mental condition, rather than by acting directly as a hemostatic.—*Courtesy R. J. Main.*

MEAKER, S. R., C. H. LAWRENCE, AND S. N. VOSE

Practical details in the management of sterility, with special reference to endocrine factors. *New Eng. Med. J.* 230: 755. June 22, 1944.

Certain abnormal conditions recognizable as obstacles to human fertility are discussed. These include constitutional depressions as well as disorders of the reproductive organs. In the

typical clinical case of involuntary sterility several of these factors may be present, and they are usually divided between the husband and the wife. This paper discusses the methods of complete diagnostic study prerequisite to any well organized plan of treatment.—*R.B.G.*

#### PRESCOTT, F., AND M. BASDEN

Inhibition of lactation by hexestrol dipropionate. *Brit. Med. J.* 2: 428. Sept. 30, 1944.

A single intramuscular injection of 12.5 mg of hexestrol dipropionate inhibited lactation in 66 per cent of a series of 44 mothers shortly after childbirth. When given within the first three days of delivery lactation did not occur, and there were no signs of breast engorgement or discomfort. Of the remaining 34 per cent about 2 per cent ultimately responded to repeated injections. Only 18 per cent required treatment for more than three days. A further course of injections, given to suppress "secondary filling," was necessary in only 7 per cent of the cases. This compares well with the figure of 25 to 45 per cent for stilbestrol. Hexestrol dipropionate, given intramuscularly in one or two doses, was effective in suppressing lactation in five cases in which it had already been established. Hexestrol dipropionate given by mouth is not so satisfactory as when given by injection.—*R.B.G.*

#### RAMOS, PERALTA A.

Membranous dysmenorrhea as a factor in sterility. *Obst. y Ginec. Latino Am.* 1: 117. 1943.

The author presents a review of membranous dysmenorrhea. He states that the maximum pain is experienced in association with the highest estrogen and lowest progesterone levels. Three patients were treated with anterior pituitary extract alone or with this and progesterone intermenstrually and chorionic gonadotropin during the period. They all experienced relief of pain and became pregnant.—*J.Z.*

#### REPORT OF ROYAL SOCIETY OF MEDICINE

Stilbestrol for advanced breast cancer. *Brit. Med. J.* 2: 20. July 1, 1944.

The treatment by stilbestrol of nearly 100 cases of advanced carcinoma of the breast was discussed by several speakers at a meeting of the Section of Radiology, Royal Society of

Medicine. In the whole series recorded by the various speakers there were 69 patients under the age of 58; of these 43 had not improved, and none showed spectacular improvement. Of the 52 patients over 58, at least 17 had improved, and 6 or 7 were reported as showing spectacular improvement amounting in some cases to a complete disappearance of fairly advanced disease. What had been presented was regarded only as a preliminary experiment to determine whether the investigation was worth pursuing.—*R.B.G.*

RIO, JOSÉ O., AND JOSÉ PENHA GODOY D'ALEMBERT

The influence of menstruation on the incidence of epileptic attacks. *Arq. Assistencia Psiquiatrica S. Paulo* 7: 449, 1942.

In 104 cases studied it was found that 57.7% experienced an increase in seizures during menstruation, which was in most cases compensated by decreases in the pre- and post-menstrual time. The influence of menstruation is most marked at the age from 26 to 30 years. It is most noted in the severe cases having a high incidence of attacks, and in quiet and poorly nourished patients.—*A.E.M.*

SHAPIRO, H. A., AND H. ZWARENSTEIN

Correspondence—The use of the South African frog pregnancy test. *Am. J. Obst. and Gynec.* 48: 740, 1944.

The authors point out that the original report concerning this technique was published by them in October, 1933, in the Proceedings of the Royal Society of South Africa.—*E.C.H.*

WOLMAN, I. J.

Urine analysis in pediatrics, ten years' progress. *Am. J. Med. Sci.* 208: 767, 1944.

This review surveys the advancements in urinalysis which are of importance in the medical management of pediatric patients. Sections are devoted to: proteinuria; sediment counts (Addis); melituria (including a discussion of: a) techniques for recognition and identification, b) alimentary melituria, c) renal glycosuria, d) lead poisoning, e) intermittent glycosuria, f) diabetes mellitus, g) essential pentosuria, h) fructosuria, i) galactosuria, j) sucrosuria, k) glycogen storage disease (Von Gierke), and l) the Fanconi syndrome. Also discussed are the

sulfonamides, pigments, and the findings in newborn and premature infants. There is a section on miscellaneous items including a discussion of: a) acetone, b) amylase, c) calcium, d) chlorides, e) cystine, f) indican, g) phenylpyruvic oligophrenia, h) 17-ketosteroids, and i) tyrosine and phenylalanine.—*E.C.R., Jr.*

## HYPOPHYSES

HEMPKILL, R. E., AND MAX REISS

Pituitary cachexia treated with corticotrophic hormone. *Brit. Med. J.* 2: 211, Aug. 12, 1944.

A case of clinical pituitary cachexia in a nulliparous woman is described. Clinical and hormone studies indicated extreme hypopituitarism. Treatment with corticotrophic hormone resulted in complete restoration of weight and cosmetic features. The authors did not believe this case to be one of anorexia nervosa. The authors suggested that in this type of case there was a sudden functional reduction in pituitary activity later followed by the physical symptoms of hypopituitarism. The suggestion was made that the picture of pituitary cachexia without structural changes in the pituitary itself may follow the menopause.—*R.B.G.*

## PANCREAS

BANYAI, A. L., AND A. V. CADDEN

Diabetes and tuberculosis. *Arch. Int. Med.* 74: 445, 1944.

An analysis of the reports of ten American clinicians based on the observations of 17,358 cases of diabetes indicates a higher incidence of tuberculosis in diabetic persons than in the general population of the United States. It is reasonable to believe that the increased susceptibility of diabetic patients to tuberculosis is due to a complexity of causes. On the basis of available clinical and experimental data we are of the opinion that hypovitaminosis A may have a significant rôle in this respect. The fact that an unusually high percentage of diabetic patients who acquire tuberculosis are not adequately treated for their pulmonary disease before it reaches the far advanced stage calls for an urgent revision of the diagnostic approach to this problem. For the recognition of early tuberculosis it is necessary to anticipate this disease. All diabetic patients should be tested with tuberculin and the test should be repeated periodi-

cally on all patients with negative reactions to tuberculin. A roentgenogram of the chest should be taken for all patients with positive reactions at least once a year. Adequate search for tubercle bacilli should be carried out when sputum is available or when roentgenologic observations justify repeated aspirations of the fasting gastric contents. In tuberculosis diabetic patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg. per 100 cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned. The results in this group of patients compare favorably with those recorded for tuberculous patients whose blood sugar was maintained on practically a normal level.—*I.B.*

BELLOWS, J. G.

The crystalline lens in diabetes mellitus. *Arch. Ophthalmol.* 32: 498. 1944.

Disturbances of the eye in diabetic patients are extremely common. The lens and the retina are most frequently affected. Two types of abnormalities of the lens appear: (1) transitory refractive changes and (2) diabetic cataract. The transitory changes are equally distributed throughout all age groups. Occurring only in cases of fresh diabetes with a high level of blood sugar and with glycosuria, diabetic myopia is less common and less in degree than diabetic hyperopia. The hyperopia always follows the myopia before a return to a normal refractive state can occur. Hyperopia, on the other hand, may arise without a preceding myopia. Most authors attribute the opacity to an osmotic or a toxic action of the excessive dextrose and its metabolic products.—*Author's Summary.*

BLOTNER, H.

Effect of prolonged physical inactivity on tolerance of sugar. *Arch. Int. Med.* 75: 39. 1945.

A study was made of the effect of prolonged physical inactivity on the dextrose tolerance of 86 nondiabetic patients—70 adults and 16 children—who had been confined to bed for from one month to 13 years by various pathologic conditions. A comparison was made between the dextrose tolerance of these patients and that of active adults and children. In general the sugar tolerance was diminished in the patients

who had been confined to bed. The fasting blood sugar ranged from 70 to 130 mg. per 100 cubic centimeters, and the fasting urine was free from sugar. After the ingestion of dextrose the concentration of blood sugar rose to abnormal levels, the maximum being 364 mg., and varying amounts of sugar were found in the urine at various times. In many of the adults there was a high renal threshold for dextrose. In patients who later became ambulatory for several months the sugar tolerance returned to normal. Hypertension, vascular disease, obesity and infection in themselves did not appear to be significant as causes. The arteriovenous differences in the blood sugar of a group of inactive persons after the ingestion of dextrose ranged from 15 to 50 mg. per 100 cubic centimeters, which is normal or greater than normal. These results indicate that the muscles of the physically inactive patients are capable of utilizing sugar normally. It is suggested that during prolonged physical inactivity the pancreas is at rest because in this state there is not the demand for rapid storage and utilization of sugar that there is in active persons. Consequently, there may ensue diabetic-like reactions to dextrose tolerance tests even with normal fasting levels of blood sugar.—*Author's Summary—I.B.*

BRUNSCHWIG, A., AND J. G. ALLEN

Specific injurious action of alloxan upon pancreatic islet cells and convoluted tubules of the kidney. Comparative study in the rabbit, dog, and man. *Cancer Research* 4: 45. 1944.

Alloxan, the ureide of mesoxalic acid, when injected intravenously, produced specific necrosis of islet cells in the pancreas and epithelium of the convoluted tubules of the kidneys in rabbits.

In dogs, intravenous injection of alloxan also injured specifically the islets cells and convoluted tubules of the kidney. The islet cells in these animals, however, did not exhibit the extensive coagulation necrosis observed in the rabbits.

In dogs, 200 to 500 mg. of alloxan per kg. were fatal in from 1 hour to 6 days, the animals having died with definitely elevated blood glucose and blood N.P.N. After total doses of 100 to 150 mg. per kg., the animals sometimes survived with transitory diabetes and with or without transitory, impaired renal function. In one dog a sustained diabetes mellitus (over 28 days)

without elevated blood N.P.N. was observed. Four human patients with carcinomatosis, one presenting an insulin-producing islet cell carcinoma of the pancreas, received intravenous injections of alloxan. Transitory, beneficial effects were observed in the patient with insulin-producing islet cell carcinoma, following injection of 0.6 gm. to 1 gm. per kg., in that attacks of hyperinsulinism were abolished for ten to twenty days following each series of injections, whereas before the injections he had two to five severe attacks a day. In the other three patients also, comparably larger doses of alloxan were given than in the dogs and rabbits, with effects on the blood sugar in only one instance. Hence it appears that the human subject is much more resistant to the action of alloxan than is the dog or the rabbit.—*Courtesy Diabetes Abstracts.*

STATION, JAMES C.

Clinical trial of globin insulin and other insulins with delayed action. *Lancet* 2: 269. 1944.

After these trials with globin insulin began two years ago, Colwell, Izzo, and Stryker (1942) reported that by mixing protamine zinc insulin with equal or larger proportions of soluble insulin all variations between the actions of protamine zinc insulin and insulin could be obtained. These proportions of insulin are much greater than have been used by most physicians. Because protamine zinc insulin normally contains an excess of protamine, the use of less than 50 per cent of insulin results in the 'mixtures' acting like pure protamine zinc insulin. Such results obviously have a bearing on the value of globin insulin. It was therefore decided to compare the action of globin insulin with such mixtures, as well as with protamine zinc insulin alone. Globin insulin was tested in forty-one cases of diabetes mellitus. In ten cases, the blood sugar was followed for twenty-four hours and the results compared with those obtained using protamine zinc insulin alone or combined with soluble insulin. With mixtures of protamine zinc insulin and insulin, the uniformity of the blood sugar throughout the twenty-four hours was even better than with globin insulin, hyperglycemia being well controlled with nocturnal hypoglycemia. The early sharp fall in blood sugar usually seen when soluble insulin is given alone was absent, and there seems no doubt that such mixtures do

not show the independent action of each type of insulin.—*Courtesy Diabetes Abstracts.*

ENGELHARDT, H. T., AND V. J. DERBES

Some observations on the treatment of uncomplicated diabetes. *Bull. Tulane M. Faculty* 3: 48. 1944.

For a number of years protamine zinc insulin has been used to regulate all diabetic patients in the Charity Hospital Clinic. With those patients who cannot be controlled with protamine zinc insulin alone, mixtures of unmodified insulin and protamine zinc insulin are used, beginning with 3.2 parts, respectively. The patient tests his urine before breakfast and before the evening meal. Results of the former test reflect primarily the effect of the protamine zinc insulin component of the mixture, and the before-supper sample indicates the action of the more soluble component.—*Courtesy Diabetes Abstracts.*

GASPAR, J. L.

Diabetes mellitus and pregnancy. *West. J. Surg.* 53: 21. 1945.

A review was conducted of 49 deliveries in 45 pregnant diabetic patients seen at the Los Angeles County General Hospital between 1935 and 1944. There were 19 stillbirths and 6 neonatal deaths, or a fetal mortality of 51%. A high percentage of stillborn infants was found from one to nine years before the clinical recognition of diabetes mellitus. It is suggested that glucose tolerance tests be performed on patients having unexplained stillbirths. In the majority of cases known to have diabetes before pregnancy it was found necessary following conception either to treat the patient with insulin or to increase the insulin in order to control the diabetic state. Diabetic complications while the patient was in labor and during the postpartum period were uncommon. Pre-eclampsia was found to be present in one third of the patients. No eclampsia was reported.—*J.M.*

GUIDOTTI, F. P., AND J. H. WINER

The rapid detection of sugar in urine. *Mil. Surgeon* 94: 111. 1944.

To determine the accuracy of this test, comparative series of 15,000 urine specimens were studied using both bismuth powder (galatest) and Benedict's test simultaneously.

jected parenterally for systemic effect. The author suggests that this effectiveness may be due to the fact that the drug is introduced by infiltration at the site of bacterial action, a point which can not be reached by systemic medication when the circulation is inadequate. The dramatic results in two cases are emphasized by colored illustrations. No direct influence on the patient's requirement for insulin has thus far been observed. The author concludes that penicillin is an invaluable adjunct to treatment of infections caused by susceptible organisms, and is well adapted for use in the pyogenic infections, such as carbuncles, so frequently met as complications of diabetes mellitus.—*E.C.R., Jr.*

PRUNTY, F. T. G.

Reactive hyperinsulinism. *Brit. Med. J.* 2: 398. Sept. 23, 1944.

Attention is drawn to a condition which may be termed "reactive hyperinsulinism," as opposed to hyperinsulinism due to overactivity of the pancreas as a result of tumor of the islets. A case of "reactive hyperinsulinism," manifest by an excessive post-prandial fall of the blood-sugar level, is described. The study of the case revealed the following points: 1. Absence of low fasting blood sugar before breakfast and after exercise. 2. The marked post-prandial fall in blood sugar during the glucose tolerance test, accompanied by the onset of symptoms of hypoglycemia, together with an instability of the blood-sugar-regulating mechanism for a period of two hours. This finding is in close agreement with the history obtained of the most severe attacks occurring after the largest amounts of carbohydrate had been taken for tea. 3. A slight increase in the sensitivity to insulin, the occurrence of a typical hypoglycemic attack after intravenous administration of insulin, and the spontaneous return of the blood sugar level to normal limits with disappearance of the symptoms. 4. The mildness and ease of control of the symptoms by means of reduction in carbohydrate intake. 5. The family history of diabetes and renal glycosuria.—*R.B.G.*

RICHARDSON, R., M. A. BOWIE, J. EDEIKEN, I. H. LEOPOLD AND M. NAIDE

Diabetes mellitus as observed in 100 cases for 10 or more years. *Am. J. Med. Sci.* 209: 1. 1945.

The authors present a series of 4 papers

analyzing this group of patients in terms of general observations, II. cardiac studies, ocular findings, and IV. peripheral vascular findings in 89 of the patients. This analysis was undertaken because these patients have been under close supervision for many years at University of Pennsylvania Hospital Clinic because they have been maintained on a diet in which the carbohydrate has been increased (to 200 gm.) and the fat decreased (70 to 100 gm.), compared with diets previously in general use.

I. *General Observations* (Richardson and Bowie): 1) The age and race distribution of these patients was that usually found in diabetes. Sixty-nine of this group were over 40 years of age. In the entire series, the disease was present for from 10 to 25 years. 2) The severity of the disease did not progress in at least 50% during the ten year period. Ten patients required less insulin at the end than at the beginning of the period, and of the 55 who required more insulin, a number had also received increases in diet. 3) Acidosis occurred in three of the group during the ten year treatment, although it had occurred in others prior to the ten year period. 4) There was some evidence of generalized arteriosclerosis was present in 66 patients, it was sufficiently marked to be called an entity in only 10. 5) Twenty-six patients had anemia, but of these only three had less than 4 million R. C. and less than 13.5 gm. of hemoglobin per 100 gm. of blood. 6) Chronic or repeated acute infections occurred in 39 patients. Most frequently encountered were: cholecystitis (16 cases), glomerulonephritis (9 cases) and tuberculosis (9 cases). 7) Of the whole group, 42% had slight or gross enlargement of the thyroid gland usually accompanied by physical signs. However, 10 of the women developed hyperthyroidism and were operated on successfully. All of them showed some improvement of the diabetes after operation.

II. *Cardiac Studies* (Edeiken): 1) Hypertension (systolic blood pressure 160 mm. Hg. or higher) was present in 38% of the cases, all of whom were over 50 years of age. The incidence of hypertension increased with each decade, was twice as common in women as men, and was independent of the duration, control and severity of diabetes. 2) Definite cardiac enlargement was present in only ten of the hypertensives. The incidence of about one half that observed in diabetic hypertensives. 3) The greatest

cardiac enlargement was observed in cases of ECG evidence of myocardial abnormality (with or without hypertension), and consequently there was a low incidence of ECG changes indicative of myocardial abnormality in the hypertensives without cardiac enlargement. 4) An ECG of the type frequently seen in hypertension and ascribed to left ventricular hypertrophy or left ventricular strain was not observed in any of the 38 cases with hypertension. 5) Only 3 (9.7%) of the patients under 50 years of age had abnormalities of the heart which could be attributed to their diabetic state; all had had diabetes for over 15 years. 6) The low incidence of cardiovascular abnormalities in the younger patients compared to similar studies in the literature on a high fat-low carbohydrate diet suggests the value of the high carbohydrate-low fat diet in reducing the incidence of premature cardiovascular abnormalities.

**I. Ocular Findings (Leopold):** 1) The long controlled therapy of this series of patients resulted in: a) a reduced incidence of cataracts and complicated cataracts, perhaps slightly reduced incidence of deep retinal hemorrhages and exudates (both of which tend to increase with the duration of the diabetes); c) an unchanged increased incidence of retinopathy of pigment, subcapsular "snowflake" cataracts, and superficial hemorrhages which tend to increase with the duration of the diabetes; and d) not significantly different from that in the non-diabetic was the incidence of optic atrophy, muscle palsies, optic neuritis, optic atrophy, senile type of lens change, and sclerosis. 2) Although arteriosclerosis, hypertension, diabetes, sepsis and hyperglycemia may all increase the incidence of deep punctate hemorrhages and waxy exudates, no one of them is a basic etiologic factor.

**3. Peripheral Vascular Findings in 89 of the 100 Cases (Naide):** 1) Three patients (11%) were under 50 years of age, and 30 (34%) of the 89 had evidence of peripheral arteriosclerosis. 2) Of the females, 42% had arteriosclerotic occlusive disease, as compared with 10% of the males. 3) Neuritis in the extremities was present in 31 of the 89 patients, chiefly in those with arteriosclerosis. 4) The severity of diabetes did not affect the incidence of arteriosclerosis. 5) There were no amputations in the entire group.

**Final Summary (Richardson):** In 100 patients with diabetes mellitus of ten or more years' duration and with at least ten years of

carefully supervised control by insulin and measured diets: 1) the severity of the diabetes did not increase in at least 45%; 2) the incidence of hypertension, infection, or ocular sclerosis was not influenced by the duration or the severity of the diabetes; 3) the incidence of deep retinal hemorrhages and exudates, and of superficial hemorrhages in the eyes was increased with the duration of the diabetes; 4) the incidence of cardiac enlargement in the diabetics with hypertension was about one half that observed in non-diabetic hypertensives; 5) the incidence of cardiovascular disease in patients under 50 years of age was lower than that previously found in diabetes; and 6) the incidence of arteriosclerotic occlusive disease of the lower extremities was much higher in diabetic women than in women without diabetes, and paralleled the greater frequency of coronary vessel disease in diabetic as compared with non-diabetic women.—*E.C.R., Jr.*

THOMAS, J. E., AND J. O. CRIDER

A further study of the innervation of the pancreas. The action of drugs of the atropine group. *Am. J. Med. Sci.* 208: 810. 1944.

The authors studied the secretory response of the pancreas to peptone, soap, or HCl in the intestine or to intravenous secretin in unanesthetized dogs before and after administration of atropine sulfate (0.2 mg./kg.) or of hyoscyamine hydrobromide (0.1 mg./kg.). The specific gravity and total nitrogen (mg./cc.) of the pancreatic juice were decreased by atropine or hyoscyamine regardless of the stimulus used to promote secretion. When the stimulus was soap, HCl or secretin, the volume of the secretion and the total nitrogen output were also reduced. When the stimulus was peptone, an increase in the volume of secretion usually followed the administration of either drug; the effect on total nitrogen was not constant but an increase was common. The authors point out: 1) the decreased response to secretin induced by the parasympathetic depressants is unexpected and contrary to the results obtained by others in anesthetized animals; 2) "tonic" cholinergic reflexes probably normally augment the response to secretin, 3) soap and HCl stimulate the pancreas in part through a nervous mechanism, and 4) the experiments provide no basis for conclusions regarding the mechanism through which peptone stimulates the pancreas.—*E.C.R., Jr.*



WHIPPLE, A. O.

Hyperinsulinism in relation to pancreatic tumors. *Surgery*, 16: 289. 1944.

It is obvious that the hypoglycemic state requires a careful search for the cause of the low blood sugar, and that hyperinsulinism must not be assumed to be the cause until lesions or disturbances in the liver, the pituitary, the adrenals, and the thyroid have been ruled out. In liver lesions causing hypoglycemia, the patients are gravely ill and show other obvious signs of liver damage. Similarly, the cases due to adrenal disease are not easily confused with hyperinsulinism, for the patients are usually seriously ill with Addison's disease or show signs of adrenal tumor. The low blood sugar levels associated with hypophyseal lesions are likely to cause more confusion, but they are usually associated with tumors causing headache and with visual field disturbances, and show x-ray evidence of widening or destruction of the sella turcica. In cases of hypoglycemia with hyperthyroidism, the basal metabolic rate is apt to be lower than in other cases of Graves' disease, and these patients may develop a thyroid storm after the removal of an islet tumor. For this reason, a basal metabolic determination should be done in all cases of suspected islet tumor; if the rate is above fifteen the patient should be given a course of iodine therapy, as in preparation for a thyroid operation. Finally, cases of epilepsy may mimic the syndrome of hyperinsulinism, because of the occurrence of "fits" or "spells." Electroencephalograms have proved of the greatest help in differentiating the epileptiform attacks from those seen in hyperinsulinism.

In reviewing the results of surgical therapy for islet tumors in this series, it is obvious that excision of adenomas and so-called questionably malignant tumors gives brilliant and lasting cures of the hypoglycemic state. On the other hand, in the majority of the patients in whom an islet-cell tumor was not discovered and a partial pancreatectomy was done, results

were not good—either because a tumor was overlooked in the head of the organ or because an insufficient amount of the pancreas was removed. This is demonstrated by the fact that an overlooked tumor was found at the second operation in eight patients, four of whom had been explored here the first time and the other four in other clinics. The fact that seven of the overlooked tumors were in the head of the pancreas emphasizes the importance of an adequate exposure by a transverse incision, and mobilization of the duodenum so that all parts of the head of the organ can be carefully palpated. The recurrence or persistence of hypoglycemia below the 50-mg.-per cent level after a partial pancreatectomy is almost certain evidence of an overlooked islet tumor.—*Conn. Diabetes Abstracts*.

## PARATHYROID

MOEHLIG, R. C., AND H. W. ULCH

Multiple parathyroid adenomata. The results of operative explorations with removal of the tumors. *Harper Hospital Bulletin* 2: 1-10. 1944.

A case is reported of a man, aged 62, who had had pulmonary tuberculosis 25 years before admission to the hospital, a left nephrectomy for the removal of multiple renal calculi 21 years before and subsequently developed vesicle calculus with all the signs and symptoms of hyperparathyroidism. The first operation, at which only the right side of the thyroid was explored, resulted in the removal of a parathyroid adenoma. However, the symptoms persisted as did the hypercalcemia and elevated serum phosphatase. A second operation seven weeks later failed to reveal a second parathyroid adenoma. Further studies were made, the patient meanwhile showing no improvement. At a third operation a large parathyroid tumor containing remnants of thyroid tissue was found on the left side. The patient died shortly afterward with evidence of cardiac failure.—*R.H.G.*



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## A Pituitary Insulotropic Principle<sup>1</sup>

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LAWRENCE LOUIS, Sc.D.

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Medical School, Ann Arbor, Michigan

IN A preliminary report (6) we showed that the same extract of anterior pituitary gland which is eventually diabetogenic in dogs quickly intensifies the hypoglycemia of human patients suffering from organic hyperinsulinism (pancreatic islet cell tumor); that the hypoglycemic effect of the extract is prompt and rapidly lost upon cessation of injections; and that the stimulus for increased production of insulin cannot be attributed to an intervening hyperglycemia since the latter never occurred. It was concluded that there exists in 'diabetogenic extracts' of anterior pituitary gland an insulotropic factor which exerts its effect directly upon the islands of Langerhans, and that this factor may be identical with that which initiates islet cell

degeneration in some species. The details of our experiments are herein recorded.

### METHODS

#### Human subjects

Two patients, one male and one female, suffering from severe and persistent spontaneous hypoglycemia resulting from chronic endogenous hyperinsulinism (excessive amounts of functioning islet tissue) were used as the subjects of this investigation.<sup>2</sup> Both patients satisfied all of the clinical and laboratory criteria necessary for the diagnosis of organic hyperinsulinism (7). In one case the diagnosis was subsequently proven at operation, at which time a pancreatic islet cell tumor was removed with a resulting complete cure of the entire disturbance. The other patient refused operation. Both had been having frequent periods of unconsciousness with blood sugar

<sup>1</sup> Presented in part at the sixteenth annual meeting of the Central Society for Clinical Research, Chicago, November 5, 1943.

The expense of these studies was defrayed in part by grants from the Horace H. Rackham and Mary A. Rackham Foundation and the Eli Lilly Company.

<sup>2</sup> For detailed case histories see appendix.

levels ranging between 12 mg. and 30 mg. per 100 cc. of blood.

### Diet and blood sugar determinations

Since in organic hyperinsulinism the average fasting blood sugar level is the most important single criterion of severity (while the patient is eating a constant diet and activity is minimal), a daily pre-breakfast blood sugar determination was done throughout the entire period of study. Serial glucose tolerance

Kjeldahl method. Stool nitrogen was assumed to represent 10 per cent of the int.

### Preparation of extract

A crude, saline extract of fresh, frozen anterior pituitary glands was prepared according to Young (30). Fractional precipitation produced a clear solution (to be the subject of a later report); 1) having a marked diabetogenic effect in normal dogs; 2) capable of producing permanent diabetes in nor

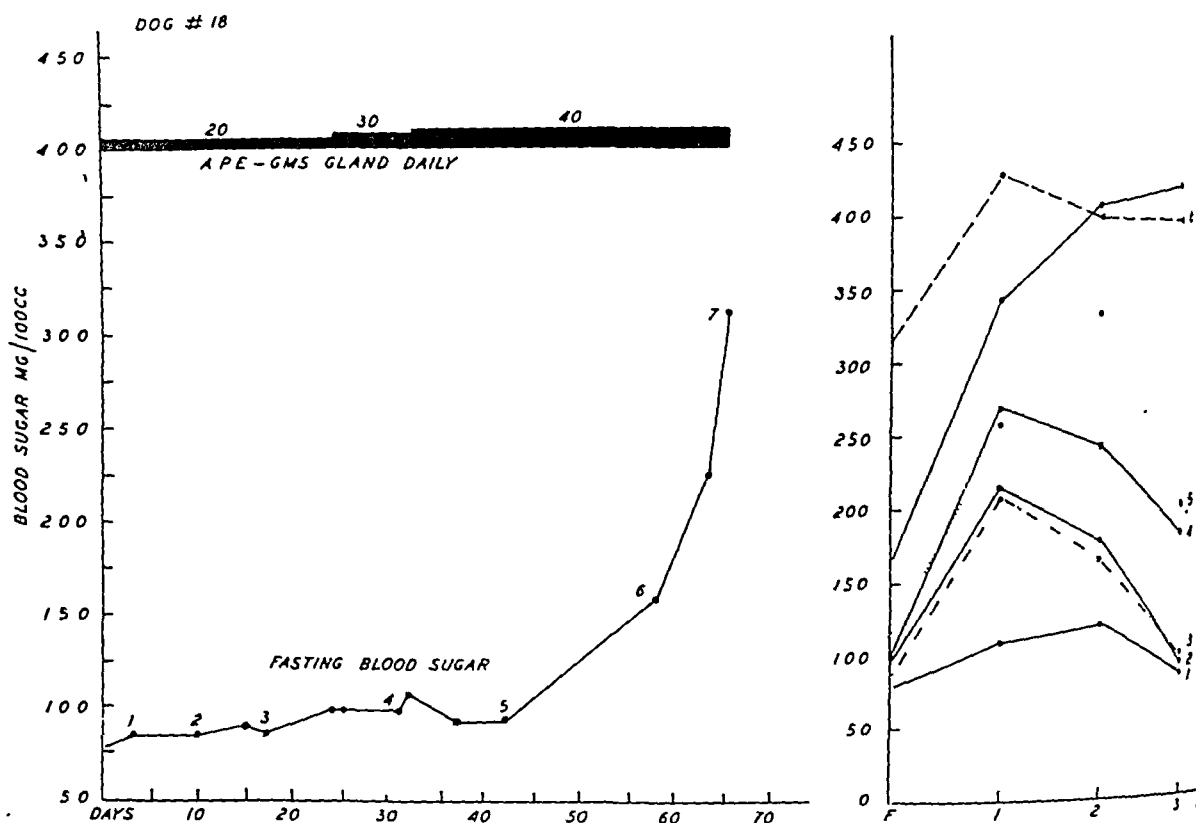


FIG. 1

curves were obtained during various phases of the work. Blood sugar was determined by the Benedict method (1). A constant weighed diet containing 80 gm. of protein, 300 gm. of carbohydrate and maintenance calories was fed.<sup>3</sup>

### Nitrogen determinations

Nitrogen balance studies were conducted in patient, A. P., for 87 of the 92 days of study. Urinary nitrogen was done by the

dogs by daily intravenous injections; and producing no untoward reaction in dogs when given intravenously daily for over 200 days. All extracts used in the patients were determined to be bacteriologically sterile and were administered subcutaneously. Chemical procedures, storage, and Berkfeldt filtration were carried out at temperatures below 4°C. Extracts more than seven days old were not used.

Dog #18 (Fig. 1) is presented as an example of the response obtained in dogs to daily intravenous injections of the same extract that was used in the patients. This animal

<sup>3</sup> In patient A.P. the following diet (P—50 gms. CHO—50 gms., cal. 1200) was fed for a short period in order to compare its effect on the fasting blood sugar level with that of the standard diet.

chosen as the example because the time required to produce an elevation of the fasting blood sugar level was somewhat longer than the average, and allowed time for serial glucose tolerance tests to indicate a "pre-diabetic" state.<sup>4</sup>

Note that between the 42nd and 60th day of injection, the fasting blood sugar rose to the level usually observed in the completely depancreatized dog; that when the normal fasting blood sugar level was finally 'broken through,' the subsequent rise was sharp and progressive. It is significant that long before the fasting blood sugar level began to rise, evidence of decreasing tolerance for carbohydrate was apparent from the serial glucose tolerance curves. It is thus clear that the extract employed is definitely diabetogenic when administered to dogs.

Figure 2 shows the results obtained in the first patient studied (A. P., male, aged 27).

*Periods I and II* contrast the effects on the fasting blood sugar level of a diet low in carbohydrate and protein with that obtained on an average normal diet. During all subsequent periods the diet eaten was identical with that ingested during Period II.

*Period III.* The daily injection of an amount of extract equivalent to ten grams of fresh anterior pituitary gland resulted in a precipitous fall of the fasting blood sugar level. The average is comparable to that obtained on the low carbohydrate diet.

*Period IV.* An abrupt rise of the level of the fasting blood sugar occurred when the extract was discontinued.

*Period V.* For the next 23 days the subject received daily injections of extract equivalent to 40 grams of fresh gland per day. Again a sharp fall of the fasting blood sugar level was obtained. There was some tendency for the level to rise in the latter half of the period (second half—av. 34 mg. per cent, first half—av. 29 mg. per cent).

*Period VI.* (Fig. 3). This three day 'rest period' is too short to place much significance on the average level of 42 mg. per cent. It is interesting, however, to note that the rise of the fasting blood sugar upon cessation of injections was not as acute as that observed

upon cessation of the first series of injections (the transition from Period III to Period IV).

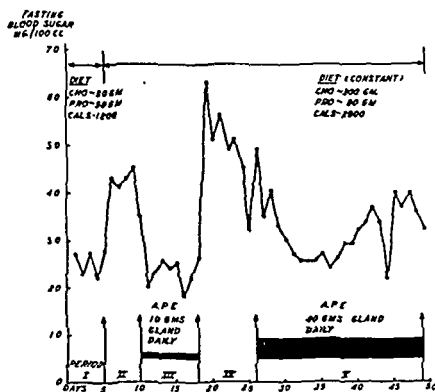


FIG. 2

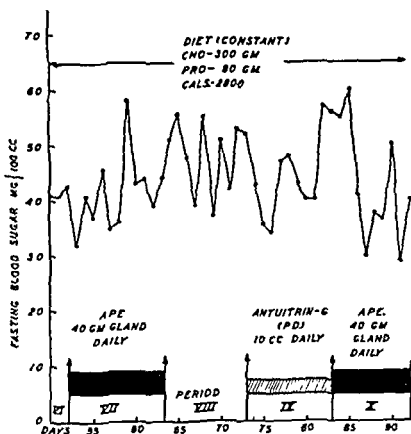


FIG. 3

*Periods VII, VIII, IX and X* did not give the clear response obtained in the earlier periods. The A.P.E. periods (VII and X) gave average levels of 41 mg. per cent and 42 mg. per cent respectively; rest period (VIII) 48 mg. per cent and antuitrin G period (IX) 44 mg. per cent. While the trend of each response is in the same direction as those obtained in the first five periods, the magnitude of each change is too small to be significant. This lack

<sup>4</sup> To be the subject of a later report.

of responsiveness in the later periods may be due to the gradual development of an anti-insulotropic factor. Such a phenomenon is recognized as occurring under similar circumstances. (See discussion).

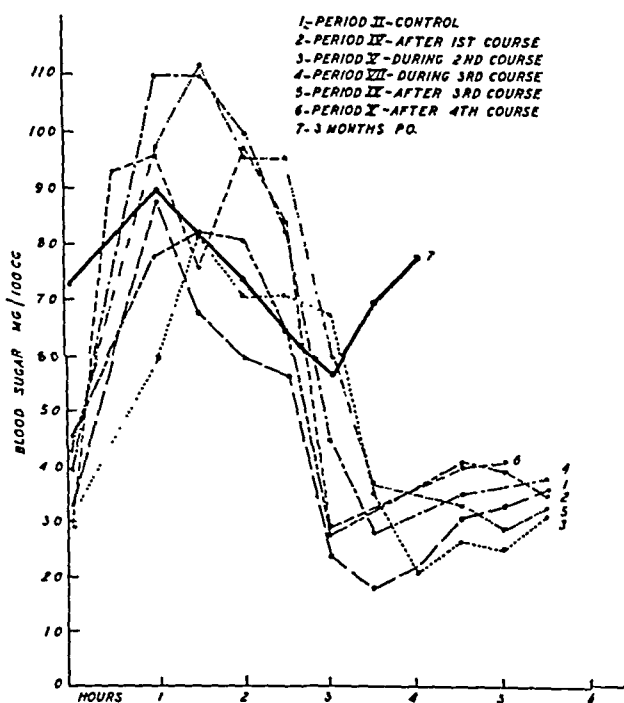


FIG. 4

### Dextrose tolerance curves

Serial dextrose tolerance tests (Fig. 4) done before, during and after various courses of A.P.E. injections gave essentially the same response each time (curves 1 through 6). Of special significance is the fact that even after the ingestion of 100 grams of dextrose (given as the test dose each time) the blood sugar never exceeded 110 mg. per cent.

### Nitrogen balance

Throughout all periods (except Period I) continuous nitrogen balance studies were made. The subject remained essentially in nitrogen equilibrium during the entire period of study.

### Microscopic pathology of surgical specimens

Dr. C. V. Weller reported on the pathology of the specimens as follows:

1. *Liver biopsy*—"Liver tissue is practically normal."

2. *Pancreatic tumor* (Figs. 5 A and B)—"Locally infiltrating adenocarcinoma. The

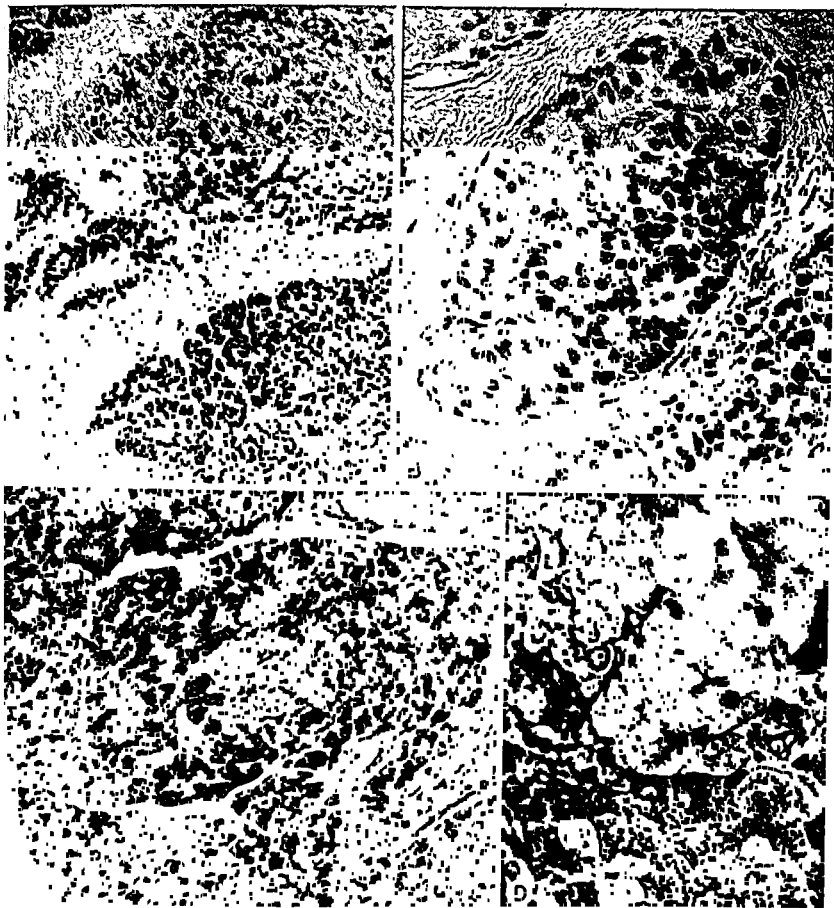
carcinoma grows in the form of cords but unusually gland-like for an islet cell carcinoma. In the pancreatic tissue about the plasma, islets appear in the usual frequency in the body of the pancreas. The islets are of normal size with a reduction in size due to the reduction in size of individual islet cells.

3. *Biopsy of pancreas* (taken from a portion close to the head of the pancreas, Fig. 5, C and D)—"In sections of a block of pancreas fixed in Zenkers' fluid and stained with fuchsin-methyl green, there is a clear differentiation between alveolar epithelium and islet cells. Between the alveoli and sometimes encroaching upon them, there are small clusters of cells which tinctorially indistinguishable from the islet cells. They have the same pale staining cytoplasm as the islet cells while less well supplied with granules, so that granules as are present cannot be distinguished from those of the islet cells.

In the islets proper there is no increase in connective tissue. Islets appear somewhat smaller than normal and their cytoplasm is very pale as compared with that of the alveolar epithelium. There is a small but prominent nucleolus in a palely stained nucleus. In the cytoplasm minute greenish gray granules or slightly larger fuchsinophilic granules occur in moderate numbers."

On Figure 6 are shown the results obtained from study of the second patient (S. female, aged 41). The sharp fall of the blood sugar of the fasting blood sugar during the first course of A.P.E. injections is again demonstrated, the response being identical with that obtained in the first patient. Note the immediate and sharp return of the fasting blood sugar level upon cessation of injections (At this point the experiment had to be terminated because the patient, having experienced more frequent hypoglycemic attacks during the injection period, felt that 'treatment' was doing her no good. She refused surgery.)

The two intravenous dextrose tolerance tests on Figure 6 are the pre- and post-treatment tests. The latter was done 24 hours after the last injection. It begins with a normal fasting blood sugar level. The response to intravenously administered



FIGURES 5 A-D.

se, however, is the same as it was before P.E. injections were begun. Again there is no evidence of *hyperglycemia* at any time.

#### DISCUSSION

It is generally agreed that induction of permanent diabetes in dogs by means of injections of A.P.E. is the result of a process which places an insurmountable burden upon the functional activity of the islet tissue, *i.e.*,

stimulation to the point of exhaustion and death. But the mechanism by which this intense stimulus is brought about remains unsettled. Because of the fact that there exists in crude A.P.E. a factor which is capable of producing marked hyperglycemia in the hypophysectomized-depancreatized animal (obviously an extra-pancreatic effect of A.P.E.), it has been assumed that the initial stimulus to the islets of the intact animal is indirect; that the extra-pancreatic effect of

A.P.E. calls forth an increased production of insulin. Two possible ways by which an extra-pancreatic influence could conceivably place great pressure upon the functional activity of the islet tissue are either through continuous hyperglycemia or through the action of an insulin antagonist which, by decreasing insulin activity in the tissues, provides a stimulus for increased production of insulin.

The results of our experiments indicate that in two patients harboring an excessive amount of functioning islet tissue, the initial and primary effect of an extract of anterior

for many of the apparently contradictory results obtained in animals treated with A. From this point of view it is of interest to refer briefly to the standard experimental results of A.P.E. injections.

#### ANATOMICAL AND FUNCTIONAL ALTERATIONS OF THE ISLETS OF LANGERHANS SHOWN TO BE ASSOCIATED WITH INJECTIONS OF A.P.E.

1. Permanent diabetes with histological evidence of degeneration and atrophy of

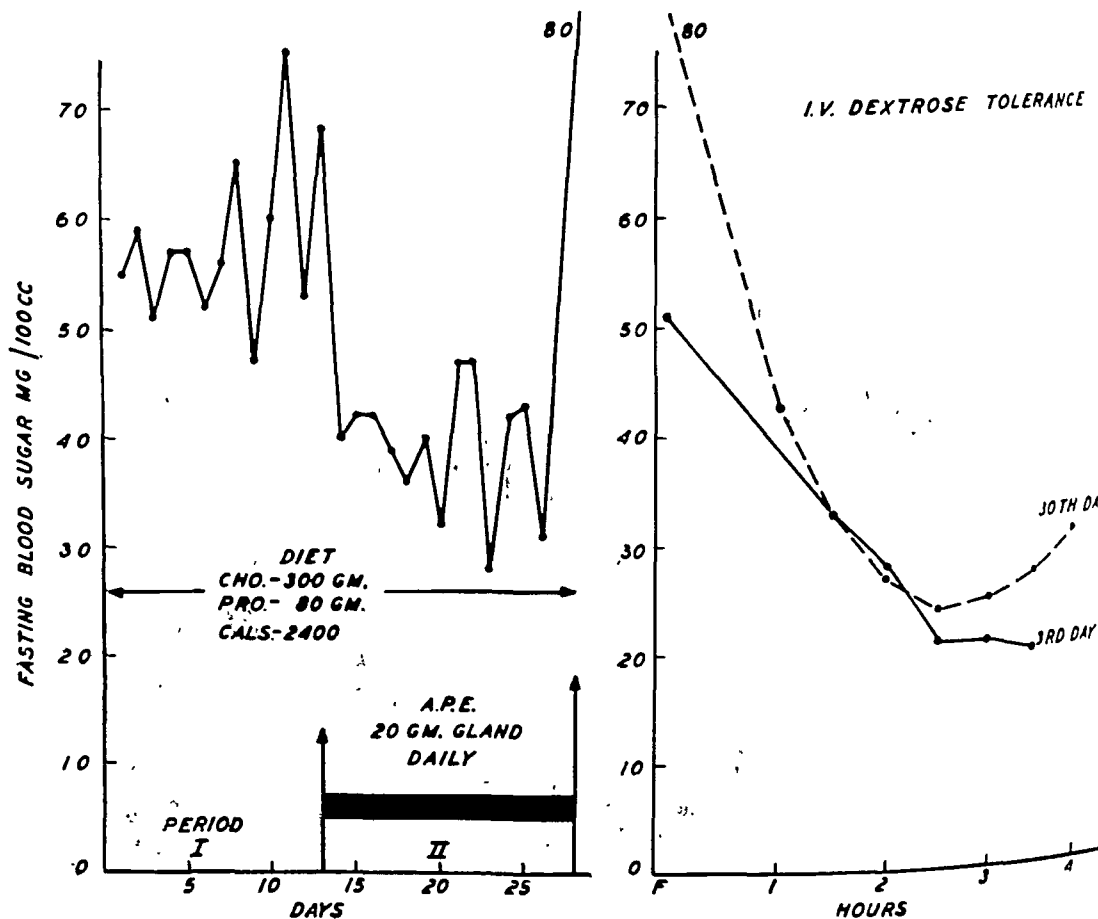


FIG. 6

pituitary gland (shown to be markedly diabetogenic in dogs) is to intensify the manifestations of hyperinsulinism. This effect occurs promptly; in the absence of any intervening hyperglycemia; and in the continued presence of excessive insulin activity. We believe that these results afford evidence of the activity of an islet cell-stimulating factor contained in A.P.E.

If one assumes the existence of such a factor, a ready explanation becomes available

tissue (4, 10, 25) can be produced in dog injections of crude A.P.E.

2. In order to establish permanent diabetes in the dog, large amounts of A.P.E. must be administered over a prolonged period of (4, 10, 24, 31, 32).

3. During the early period of such administration in the dog, unusual mitotic activity of the islet tissue is demonstrable (25).

4. In the intact dog there always occurs an initial 'resistance period' of several days

weeks before the blood sugar begins to rise. This is in sharp contrast to the quick rise of blood sugar which occurs in the A.P.E. treated Houssay dog.

5. Some dogs are totally resistant to the hyperglycemic effect of large amounts of A.P.E. Such animals exhibit evidence of normal or increased secretion of insulin following treatment (15, 24).

6. The degenerative effects of A.P.E. upon the islets of the dog can be prevented (and consequently the diabetes, also) by simultaneous administration of insulin. But evidence of increased mitotic activity of the islets is nevertheless observable (2).

7. A normal dog under treatment with A.P.E. may secrete ten to twenty times the normal amount of insulin long before he develops hyperglycemia (33).

8. The same extract which eventually causes diabetes in dogs, doubles the amount of islet tissue in the pancreas of the rat (26). More than twice as much insulin is extractable from the pancreases of the treated rats as from their untreated controls (22). Hyperglycemia does not occur during the development of this result (26).

9. Young A.P.E. treated rats have a consistently lower fasting blood sugar level than their untreated controls and within a few days after treatment exhibit a significant increase in carbohydrate tolerance without any preceding decrease in tolerance (14).

10. No one has yet succeeded in producing diabetes in the intact rat by the use of A.P.E. But the partially depancreatized rat (the pancreatectomy being insufficient in extent to produce diabetes of itself) develops hyperglycemia under such treatment (19).

11. Eighty per cent of rabbits treated with large doses of A.P.E. develop transient glycosuria which quickly disappears despite continued injections. All rabbits (whether or not glycosuria occurs) so treated "have twice as much islet tissue by weight" as their controls (23).

12. In A.P.E. treated rabbits there occurs within two hours after the first injection a fall of blood sugar of about 10 mg. per cent, but with repeated injections some go on to develop hyperglycemia (26). In one rabbit of

100 so treated the blood sugar continued to fall to the convulsive level of 20 mg. per cent as a result of four daily injections of the same crude extract which produced diabetes in others (26).

*Comment.*—We thus have evidence that the same extract which is capable of inducing diabetes under some circumstances produces functional hyperinsulinism and under others, morphological hyperinsulinism; that the initial effect of the extract is stimulatory in nature, regardless of whether the final outcome is diabetes or hyperinsulinism; and that hyperglycemia is not the initial stimulus to the islets of Langerhans.

#### THE ROLE OF HYPERGLYCEMIA IN THE PRODUCTION OF PERMANENT PITUITARY DIABETES

1. A.P.E. administered to the Houssay dog quickly produces a sharp rise of the blood sugar level, this effect obviously being an extra-pancreatic one (16). The factor responsible for this response is relatively heat stable and is incapable per se of producing hyperglycemia in the intact dog. An additional factor which is heat labile and which is present in crude A.P.E. prepared and stored in the cold, is required in order to produce diabetes in the normal dog (19).

2. Partially depancreatized cats made diabetic with A.P.E. (the diabetes persisting after withdrawal of treatment) exhibit various degrees of functional and morphological recovery of the islets when the hyperglycemia is reduced (insulin, phloridzin, etc.), provided that such procedures are applied before the hyperglycemia has persisted for more than about three months. Otherwise irreparable damage of the islets ensues (20).

3. Houssay remarks, "The (early) alterations in the islets are due to the anterior pituitary extracts and are not due to the rise in blood sugar, since they do not occur in dogs which have received glucose in a continuous intravenous injection, so as to maintain a blood sugar level as high as that of the anterior-hypophyseal diabetic dogs" (16).

*Comment.*—While it seems to be true that hyperglycemia, existing by virtue of diminished insular function, is capable of producing



further damage to the islets of Langerhans, evidence is lacking to support the view that the initial effects upon the islets during the induction of diabetes with A.P.E. is the result of an induced hyperglycemia. It would appear, in order for the stimulus of hyperglycemia to injure islet tissue, that such tissue must first be placed in a relatively exhausted state functionally (subtotal pancreatectomy, excessive stimulation with A.P.E., etc.). It is likely that under the circumstances of A.P.E. injections in the dog, a vicious cycle is set up from which the islets cannot escape, *i.e.*, (1) excessive insulotropic stimulation, (2) eventual hypoinsulinism, (3) hyperglycemia, which if sufficiently prolonged leads to (4) complete degeneration of islet tissue.

The difference in the final outcome in the dog on the one hand, and in the rat and rabbit on the other, is dependent upon the ability of the islets to keep pace with the massive stimulus, being quickly overwhelmed in the former and being able to respond in the latter. Experience with the rat (intact versus partially depancreatized) indicates that the total amount of islet tissue available to respond is an important factor in the final outcome. Thus three factors appear to determine the result: (1) the size and frequency of the stimulating dose of A.P.E., (2) the total amount of islet tissue available to respond, and (3) possible species differences in the capacity of the islet cells to respond.

Human beings with organic hyperinsulinism present a very special situation and a unique opportunity to observe the immediate rather than the secondary effects of the stimulating factor. We know in these cases, before any A.P.E. is administered, that there exists a great excess of functioning islet tissue. The blood sugar is persistently low and convulsive attacks are frequent. The reserve of islet tissue is so large that it is capable of responding at once and fully to an insulogenic stimulus. The results of our experiments are in line with this interpretation.

Theoretically, if the stimulus could be made sufficiently large in relation to the capacity of the islet tissue to respond (such as the relation between the stimulus and the

reserve supply in the dog) we should expect eventual degeneration of all islet tissue, tur-  
tissue included.

#### DIABETES MELLITUS VS. ORGANIC HYPERINSULINISM

It is conceivable that clinical diabetes mellitus and organic hyperinsulinism have common basis of origin; that organic hyperinsulinism represents the exceptional response within the species to the same stimulus of the islets which usually results in the development of diabetes.

Clinically, there is much to suggest the impairment of anterior pituitary function (X-ray irradiation, destructive processes, surgery, etc.) occurring in the course of well established diabetes results in amelioration of the disease. But *the mode of induction of the usual type of clinical diabetes remains unanswered*, involving among other variables an hereditary aspect.

In *unusual* types of clinical diabetes, on the other hand, there is a good deal of evidence to support the idea that excessive activity of the anterior hypophysis is responsible for the production of the disease. It is frequently pointed out that the high incidence of diabetes in cases of pituitary basophilism (Cushing's Disease) and pituitary eosinophilism (acromegaly, etc.) represents the clinical counterpart of the experimental induction of diabetes in normal animals by means of injections of A.P.E.

It is of considerable interest, therefore, to note that a significant number of proved cases of organic hyperinsulinism (in which complete autopsy material is available) have shown abnormalities of the pituitary gland similar to those found in association with diabetes mellitus (12, 21, 27, 28). Further clinical and pathological investigation of this relationship seems indicated. In this connection, the occasional finding of generalized hyperplasia of the islets of Langerhans in association with multiple islet cell adenomata (8, 18) suggests the activity of an islet cell stimulating substance. Frazer (11) and others arrive at the interesting conclusion that "a patient with acromegaly may be at the stage of 'co-

ensatory hyperinsulinism' or may end by having hypo-insulinism like a 'Young dog'. The term "dysinsulinism" has been suggested (13) to denote a condition in which the patient presents evidence of diabetes at one time and of hyperinsulinism at another, and in some cases, evidence of both at the same time. This situation is not a proved clinical entity. But the occasional case (17) of unquestioned diabetes which gradually becomes milder and finally ends as one of severe paroxysmal spontaneous hypoglycemia demands our attention. A similar case (3) was shown at autopsy to have developed an islet cell carcinoma. Harris (13) mentions three diabetic patients whose hyperglycemia was receded by a period of hyperinsulinism. He also states that 'the familial tendency exists in hyperinsulinism as in diabetes.' Others have commented upon the unusually high incidence of diabetes in the family background of patients with hyperinsulinism.

#### SUMMARY

Two patients suffering from organic hyperinsulinism were given daily injections of anterior pituitary extract and the response obtained was compared with that observed in dogs receiving the same extract. The results indicate that the extract employed is 'diabetogenic', when administered to dogs; that the induction of hyperglycemia in dogs by daily injections is associated with a latent period varying from several days to several weeks (a consistent finding observed by all investigators); that the same extract which eventually hyperglycemia-producing in dogs is promptly hypoglycemia-producing in humans harboring an excessive amount of functioning islet tissue; and that cessation of injections allows the blood sugar to return quickly to or above its original level. During the course of treatment with A.P.E., dogs show a gradual decrease in tolerance for carbohydrate while no decrease from the initially excessive tolerance is observable in these patients.

It is reasonable to conclude from these findings that the initial and primary response of islet tissue to the so-called "diabetogenic

principle" is one of prompt stimulation. In order that this response be brought out clearly it is necessary to have an abnormally large amount of functioning islet tissue available to respond, so that the secondary effect (islet fatigue) of an overwhelming stimulus does not soon overshadow the primary activity of the substance (as it does in the dog). This requirement is provided in patients having secreting pancreatic insulomata.

In the later periods of injection of A.P.E. in one patient neither a hypoglycemic nor a hyperglycemic effect was obtained. The fact that the fasting blood sugar level remained low indicates that excessive amounts of insulin continued to be secreted. But no further lowering of the blood sugar was obtainable, as it had been during the initial injection periods. During this same period no decrease in tolerance for carbohydrate was demonstrable to indicate that the lack of hypoglycemic response was due to islet fatigue. The only ready explanation for this finding is the possibility that an anti-insulotropic substance had been built up during the first three to four weeks of injections. This type of response to continued administration of pituitary extracts is known to occur (5, 28).

#### CONCLUSIONS

1. Crude A.P.E. prepared and stored in the cold contains an insulogenic or insulotropic principle which acts by stimulating directly the insulin producing cells of the islands of Langerhans.

2. The exhausting effect of this principle upon the islets of Langerhans is responsible for the initiation of hyperglycemia in normal dogs. This substance is not the same as that which produces hyperglycemia in the Housay animal.

3. The sequence of events during the induction of permanent diabetes in the normal dog by means of A.P.E. is (1) a direct and excessive stimulation of the islands of Langerhans; (2) a gradually diminishing ability of the islets to respond to the persistent stimulus with consequent decrease of insulin production; and (3) hyperglycemia, which, if sufficiently prolonged, carries the process of islet

cell degeneration to completion. Hyperglycemia, *per se*, constitutes a burden upon the *already debilitated islets* and may set up a vicious cycle from which the islets cannot escape.

4. When the islets are able to respond to the insulogenic stimulus with sufficient intensity to avoid being overwhelmed by it, the result obtained is not diabetes but hyperinsulinism (morphologically and functionally). This response occurs in the absence of hyperglycemia and cannot, therefore, be attributed to a stimulus stemming from an elevated blood sugar level.

5. Factors which determine whether the stimulus will result in diabetes or in hyperinsulinism are: 1, duration and intensity of the stimulus, 2, total amount of functioning islet tissue available to respond, and 3, species differences in islet tissue reactivity.

6. When conditions are such that there exists an abnormally great abundance of functioning islet tissue (as is the case in human organic hyperinsulinism) the principle response to the so-called "diabetogenic" factor becomes clearly evident. It consists of a prompt, sharp, further fall of the blood sugar level without any intervening hyperglycemia, and a rapid return when injections are stopped. This is in sharp contrast to the prolonged lag period which is necessary for the induction of hyperglycemia in normal dogs. The hyperglycemia thus produced is a phenomenon secondary to intense activity of the insulotropic substance upon the islet cells with eventual fatigue.

7. It is considered likely that clinical diabetes mellitus and, at least, some cases of organic hyperinsulinism have a common basis of origin, the latter representing the exceptional response within the species to the same insult which usually produces the former.

CASE REPORTS

*Case #1. A. P.*, aged 25, white, single laborer. Admitted 10-28-42.

*C.C.*—"Spells."

*P.I.* The patient had been perfectly well until his initial attack in August, 1941. While at work at 11:30 a.m. he suddenly became very weak and lost consciousness. He awoke spontaneously in 30 minutes

and had his lunch. There was no further trouble until a similar episode at 4:30 p.m. occurred in December, 1941.

In mid-January, 1942, attacks became more frequent and progressed in frequency and severity until the time of admission to the University Hospital. They began to occur most frequently in the early morning hours (4:00 a.m. to 7:00 a.m.) but often occurred three to four hours following the preceding meal. Premonitory symptoms were hunger, tension, weakness, sweating and visual disturbances. This was followed by a semi-lucid period during which he was aware that he could not control his muscular movements. He knew that he was unable to comprehend commands during this period although he heard them. Complete loss of consciousness was often associated with generalized convulsive movements.

He did not believe that convulsions occurred during those attacks in which he was found to be unconscious in bed before breakfast. The patient's sister with whom he was living, has a diabetic child receiving daily injections of insulin. The sister having noted the similarity of his symptoms to those of her child during insulin reaction, found that he, too, could be quickly revived by the administration of orange juice. The patient then learned that he could ward off day-time attacks by the ingestion of food if he acted promptly.

By the time of admission attacks had progressed in frequency to an average of two per week. The patient's weight had been constantly at about 150 pounds for several years.

*P.E.* The patient was a very well developed, healthy looking, young male. B.P. 100/60. No physical defects could be elicited on examination.

*Laboratory Data.* Blood counts, urine examination and Kahn tests were negative. Spinal fluid, negative. B.M.R.: -4 per cent. Serum proteins: total 7 gm. per cent, albumin 4.6 gm. per cent, globulin 3 gm. per cent. Bromsulphalein (5 mg./Kilo-30 minutes): less than 15 per cent retention. Cholecystogram showed a normally functioning gall bladder without evidence of stone. X-ray of the skull was negative. Glucose tolerance test after standard dietary preparation (8) (9) was:

F.....	31 mg. per cent
1 h.....	101
2 h.....	83
2½ h.....	77
3 h.....	52
3½ h.....	37
4 h.....	31
4½ h.....	25
5 h.....	44
5½ h.....	31
6 h.....	29

Daily fasting blood sugar values ranged from 25 to 60 mg. per cent; the majority from 25 to 35 mg. per cent. Blood sugar values during spontaneous attacks ranged from 9 to 30 mg. per cent.

After the investigative program (see text) the

n completed the patient was operated upon by F. A. Collier. A firm, round, well encapsulated ss, 1 cm. in diameter was found to be deeply embedded in the body of the pancreas. This with a surrounding portion of pancreatic tissue was removed (Figs. 5 A and B). A biopsy of the normal portion of pancreas (Figs. 5 C and D) and of the liver was obtained. (For microscopic findings see under 'sults')

The morning after operation the fasting blood sugar was 115 mg. per cent. For the next seven days was 73, 63, 98, 78, 83, 92, and 82 mg. per cent respectively. A glucose tolerance test (after standard dietary preparation) 3 months post-operatively was:

Γ	72 mg. per cent
1 h.	90
2 h.	73
2½ h.	64
3 h.	52
3½ h.	66
4 h.	74

The patient has returned to his job and has remained perfectly well for the past two years

*Case #2. B. S.,* aged 41, white, married housewife. C.C. Increasing fatigue, dizziness, and spells of consciousness

*P. I.* This patient has been followed during multi-admissions and several out-patient visits to the University Hospital since June 6, 1939. The essentials of her history are recorded below.

There had been intermittent difficulty in eating solid foods since January, 1939. For the most part she had subsisted on a liquid diet. There had been frequent periods of fatigue and dizziness. On May 1939, she had lapsed into an unconscious state in which she remained for four or five hours until 'I. V. fluids' were given at a local hospital. Admitted on the Otolaryngology Service on June 6, 1939, for correction of esophageal obstruction, she was found to have

She remained well until April, 1941, when fatigue, ziness, irritability and drowsiness began to appear in attacks. On May 16, 1941, several teeth were extracted by her local dentist. That evening she became semi-stuporous but recovered in two hours. Two years later a similar attack led her local physician to refer her a total of 70 units of insulin (50 u. and 20 u.). She was sent to University Hospital in a semi-comatose state. She had gained from 140 to 186 lbs. in the interval. Consciousness was quickly restored by means of intravenous glucose. For the next two days the fasting blood sugar was 28 mg. per cent and 23 mg. per cent respectively. During a spontaneous attack at 1:00 p.m. on the third day the blood sugar was 22 mg. per cent. Oral glucose tolerance test after seven days of standard dietary preparation (8, 9) was follows:

F.	49 mg. per cent
½ h.	66
1½ h.	107
2 h.	108
2½ h.	104
3 h.	87
3½ h.	48
4 h.	38

During this admission cardiospasm again became a serious problem but was well controlled by the use of nitroglycerine sublingually before meals. It was noted that the cardiospasm was intimately related to the hypoglycemia, never occurring unless the blood sugar first became low. She was advised to remain for the various tests designed to exclude other possible causes of spontaneous hypoglycemia. She was told that she probably had a pancreatic adenoma which would require surgery. She asked to be discharged.

Her final admission to the University Hospital was eighteen months later (11-18-42). In the interim she had been eating well, having gained 17 pounds more (wt. now 203 lbs.). She had been continuously aware of mid-morning and mid-afternoon weakness, but had had no other symptoms until one month before. At that time attacks of unconsciousness, lasting from 15 minutes to several hours, began to occur again, usually coming on in the early afternoon or evening. Such an attack would always occur, if for any reason she missed a meal. For the past two weeks attacks had been occurring daily. The day before admission she had been unconscious from 1:00 p.m. to 6:00 p.m. The attack had been terminated by the administration of glucose intravenously.

*P. E.* The patient was a very obese woman (5' 4"—203 lbs.) who did not appear ill, but who exhibited marked emotional lability. The B.P. was 138/92. The only abnormal physical findings besides the obesity were, 1. an adenomatous thyroid, and 2. hyperactive reflexes

*Laboratory data* Blood, urine and Kahn reaction were negative. Blood bilirubin 0.3 mg. per cent. Hippuric acid test (I.V.—1 hour) 1.16 and 1.28 gms. Bromsulphalein (5 mg./Kilo—30 minutes) 10 per cent retention, N.P.N.—20 and 30 mg. per cent. Serum proteins—total 6.6 gm. per cent, albumin 3.1 gm. per cent, globulin 3.5 gm. per cent. Cholecystogram showed non-visualization of the gall bladder without evidence of stone. B.M.R. plus 3 per cent.

At this point our studies were begun (See Text). At the conclusion of the studies operation was refused and the patient was discharged against advice.

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# Observations on 78 Thyrotoxic Patients Treated with Thiouracil

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INASMUCH as nearly 12 per cent of all cases treated with thiouracil have shown reactions of lesser or greater degree (38) it seems essential to collect data from large groups of patients before giving unqualified support to its widespread use. We reviewed

Forty-one patients were allowed to continue their usual routine of living. The remainder were hospitalized for long or short periods to permit continuous observation and more thorough investigation. Except for their confinement in the hospital these patients

TABLE 1. AGE AND SEX DISTRIBUTION IN 78 CASES OF THYROTOXICOSIS TREATED WITH THIOURACIL

Type of goitre	Total No.	Male			Female		
		No.	Age (yrs)		No.	Age (yrs)	
			Range	Av		Range	Av.
Hyperplastic	53	6	25-64	46.5	47	14-65	40.1
Nodular	25	4	46-65	50.7	21	31-67	47.7
	78	10			68		

the entire literature to June 1, 1944 (38). Since that time at least 58 articles on thiouracil have appeared (3-38, 40-42, 44-52, 54-64), of which 34 (3-7, 9-11, 14-16, 19, 22, 23, 25-27, 29, 30, 34-38, 40-44, 46, 50-52, 57, 59-62) summarize data from not less than 60 patients.

## I. MATERIAL AND METHODS

Ten male and 68 female patients with thyrotoxicosis were studied while under treatment with thiouracil<sup>2</sup> (Table 1) for periods ranging from two weeks to 16 months (Table 2).

TABLE 2. TREATMENT OF 78 THYROTOXIC PATIENTS WITH THIOURACIL

Months of treatment	No cases under treatment	Treatment		Remarks
		Discontinued in	Resumed in	
0	78			
1/2	76	2	0	1 operated
1	68	8	3	1 toxic
2	59	7	1	5 operated
3	52	3	3	1 operated
4	45	1	0	
5	42	2	1	
6	37	2	0	
7	28	3	0	1 operated
8	19	4	1	
9	18	1	1	
10	14	1	1	
11	9	0	0	
12	7	0	0	
13	4	0	0	
15	3	0	0	
16	0	0	0	

<sup>1</sup> Emmanuel Maynz Fellow in Research.

<sup>2</sup> Thiouracil used in the pursuit of these studies was furnished through the courtesy of Drs. B. W. Carey and Anton M. Hardy of the Lederle Laboratories, Pearl River, N. J.; their kindness is gratefully acknowledged.

were encouraged to conduct themselves as they would at home; no special diets, periods of rest, or drugs (with the exception of thiouracil) were used.

Various routines for the administration of thiouracil have been used in the course of these studies, but that which is now commonly employed follows:

TABLE 3. DAILY DISTRIBUTION OF THIOURACIL MEDICATION

Total dose daily		2 tablets given at	1 tablet given at
gm.	tab.		
0.8	8	7 a.m. and 10 p.m.	10 a.m. and 1, 4, and 7 p.m.
0.6	6	0	7 and 10 a.m., and 1, 4, 7 and 10 p.m.
0.4	4	0	7 a.m., 12 noon, and 5 and 10 p.m.
0.3	3	0	7 a.m., 2 and 10 p.m.
0.2	2	0	8 a.m. and 8 p.m.

Other features of the regimen, including a description of laboratory methods, have been previously described (38, 53).

II. RESULTS

A. Change in subjective symptoms and physical findings

The more commonly mentioned symptoms and observed signs are included in Table 4. A "sense of well being" was usually experienced by the patient long before specific subjective complaints or objective phenomena showed any appreciable change. This ill-defined feeling of improvement has been known to make its appearance as early as the third day, and was usually present by the end of the first week. The term "nervousness" was used quite loosely by most patients and in some instances could not be further clarified or amplified.

The pulse rate was almost invariably lower after treatment, although in 4 instances it did not return to normal, even after several months of care. One of these four patients was in severe cardiac failure when treatment was begun. The other three showed no clinical or electrocardiographic evidences of myocardial damage, although some may have

been present. Of the 30 patients with a pre-treatment systolic blood pressure exceeding 150 mm. of mercury, three had a known history of essential hypertension. The remaining 27, in whom the pressure did not fall below 150 mm. of mercury under treatment, were believed to be suffering from a benign form of hypertension, as the diastolic pressure in each instance was 90 mm. of mercury or lower. Exophthalmos was present in 38 of the patients (Tables 4 and 5). In no instance was an increase in the exophthalmos observed under treatment. This may simply mean that we had no instances of the thyrotrophic effect of exophthalmos in the entire series of cases (43).

TABLE 4. CLINICAL FINDINGS IN 78 THYROTOXIC PATIENTS TREATED WITH THIOURACIL

Symptoms and signs	Number of Patients			
	Initially present	Not mentioned	First symptom to disappear <sup>1</sup>	Abnormal after treatment
"Nervousness"	78	0	35	78
Apprehension	62	16	29	62
Palpitation	44	13	14	44
Insomnia	38	24	17	38
Voracious appetite	45	22	3	45
Anorexia	11	22	0	11
Weakness	19	49	0	19
Diarrhea	7	0	0	7
Sweating	65	8	0	65
Pulse above 100	52	0	0	48
Systolic B.P. above 150 mm. Hg.	30	0	8	22
Pulse pressure greater than diastolic pressure	26	0	0	16
Loss of weight	78	0	18	72
Enlarged thyroid	65	0	0	26
Exophthalmos	37	0	0	17
Fibrillation	18	0	0	15

<sup>1</sup> In some instances two of these were believed to disappear simultaneously or nearly so.  
<sup>2</sup> Decreased only—see tab. #6.  
<sup>3</sup> Decreased only—see tab. #5.

An initially large thyroid gland was encountered in 65 patients, of whom 41 had a hyperplastic, and 24 a nodular goiter (Table 6).

The fibrillation present in 18 cases prior to treatment was believed to reflect, at least in part, the abnormal cardiac load arising from the thyrotoxicosis. Digitalis was pur-

TABLE 5 EXOPHTHALMOS IN 78 THYROTOXIC PATIENTS TREATED WITH THIOURACIL

	Hyperplasia				"Adenoma"			
	Total No cases	De creased	Un changed	In creased	Total No cases	De creased	Un changed	In creased
Before Treatment	29	—	—	—	9	—	—	—
Under Treatment	26	13	13	0	9	4	5	0
B M R still high when observation made	—	4	1	0	—	0	1	0
Effect of Treatment not mentioned	3				0			

not given to any of these patients until the thyroid condition was brought under control, and then only if the fibrillation had failed to disappear under thiouracil therapy alone. In six of the ten patients with hyperplasia, a normal rhythm was resumed under thiouracil therapy alone. In one of these, a Wilson type of bundle branch block was present which was not influenced by the thiouracil. Two of these ten patients developed a normal rhythm when digitalis was added, and in two the fibrillation remained unchanged despite both thiouracil and digitalis. In the nodular group six of eight patients developed a normal rhythm under treatment with thiouracil alone, one more reverted to a normal sinus mechanism when digitalis was also administered, and one remained resistant to both types of therapy. Under previous therapy with digitalis and iodine in four of the hyperplastic variety and in two of the nodular type of goiter, no change in the associated fibrillation had been obtained.

Previous operation had been performed in

10 of the 53 patients with a hyperplastic goiter and in 8 of the 25 with a nodular gland. Multiple operations had been done in three patients. These surgical procedures appeared to exert no influence upon the action of thiouracil in relieving all toxic manifestations of either type of goiter.

#### B Laboratory data

The correlation of objective clinical and laboratory data are well illustrated in Figure 1, (case No. 64). This figure graphically describes the case of a 44 year old woman, whose symptoms had started two years prior to the beginning of therapy. Since that time she had complained of palpitation, cold clammy perspiration particularly of the hands and feet, and nervousness. She was 60.25 inches tall and despite a 10 pound loss of weight in one year was still much overweight at 154 pounds. Eye signs of thyrotoxicosis were absent. The confirmatory findings included a diffuse soft enlargement of the thyroid, a fine tremor of the tongue and hands, tachycardia (initial

TABLE 6 CHANGES IN THE SIZE OF THE THYROID WHILE UNDER TREATMENT WITH THIOURACIL

Status of gland	Hyperplasia			"Adenoma"		
	No cases	Average		No cases	Average	
		Mos of Rx	B M R when change noticed		Mos of Rx	B M R when change noticed
Initially						
Large	41	—	—	24	—	—
Normal	9	—	—	0	—	—
Scarred	3	—	—	1	—	—
After Treatment						
Further enlargement	11	2.8	+4.6	10	5.3	+3.1
Decrease in size	14	0.9	+9.1	6	0.7	+22
Decrease and then increase	2			2		
Not mentioned	6			2		



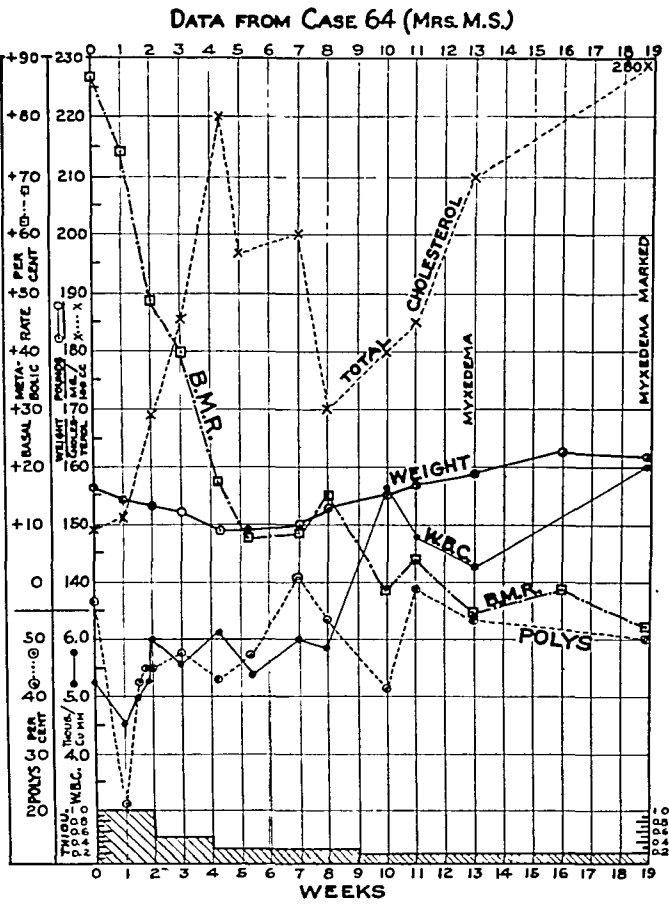


Fig. 1

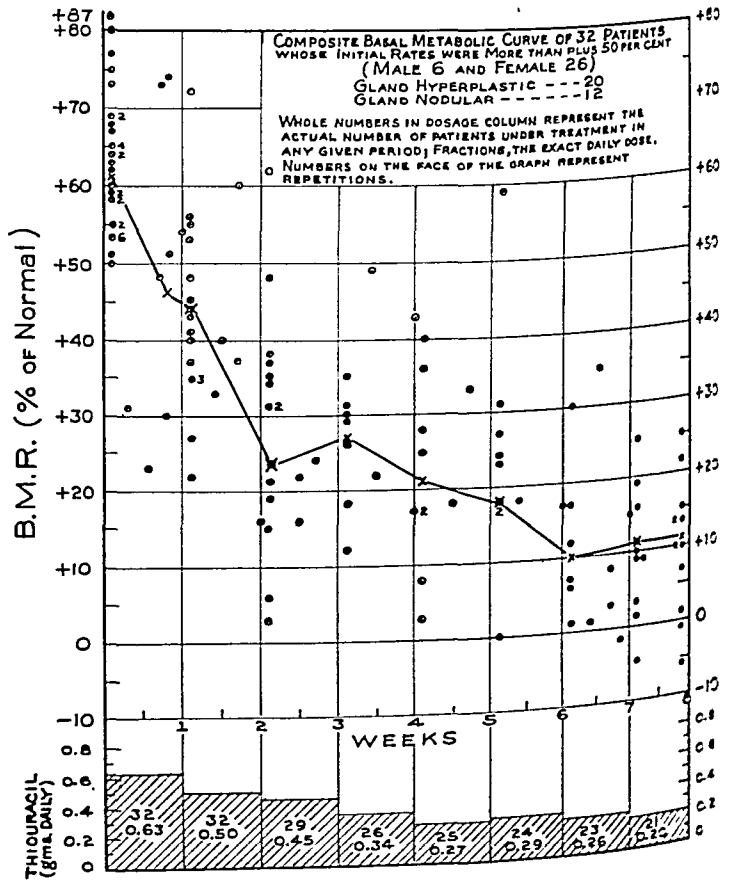


Fig. 2

(rate 140 per minute), hypermotility of the heart, and hyper-active reflexes. The patient was believed to have a forme fruste type of toxic hyperplasia. Under treatment it will be noted from Figure 1 that the basal metabolic rate and the blood cholesterol moved inversely to each other, and that the cholesterol exceeded high normal levels while the metabolic rate was still plus 18. A later adjustment took place in this figure only to give way to abnormally high values as a myxedematous state was reached. Moreover, it seems important to emphasize the fact that myxedema occurred when the basal metabolic rate was minus 8. The weight changes in this case are rather typical with an initial decrease and subsequent increase, although in underweight individuals the increment often begins somewhat earlier, *i.e.* in the second week. The decrease in weight during the myxedematous phase was seen in all of the four patients who developed the condition and is thought to be due to the heightened irritability, nervousness and insomnia which occurs.

The marked decrease in the leucocyte and polymorphonuclear cell counts occurred at the end of the first week, in *Case number 64*, that is somewhat earlier than usual (Fig. 1). Treatment was not stopped because of the rapid return to normal within 24 hours, and the complete absence of subjective symptoms commonly seen in the toxic or hypersensitivity individual. Notice the slight increase in the total number of white blood cells appearing in the tenth week of treatment. This is a common phenomenon frequently occurring immediately after a depression at any time during treatment and commonly much more pronounced than seen here.

### 1. The basal metabolic rate

Composite curves of serially taken basal metabolic rates in the hyperplastic and nodular groups revealed no difference in the speed with which the two groups reacted to thiouracil. However, when we compared the group of individuals which had basal metabolic rates above 50 with those below that figure, it was obvious that the drop in the former on a percentage basis was much greater during

the first two weeks than was that of the latter (Fig. 2 and Fig. 3).

### 2. Blood cholesterol

Initial values for blood cholesterol were high, *i.e.*, above 200 mg. per 100 cc., in 11 of 52 patients upon whom performed. All of these had satisfactory evidence of thyrotoxicosis, but in two the high cholesterol could have been attributed to an uncontrolled diabetes. In 36 patients, serial examinations were made while patients were under treatment. In 31, these studies were done at approximately two week intervals until the thyrotoxicosis was controlled and less frequently thereafter.

The relation between the concentration of cholesterol in blood and the degree of elevation of the basal metabolic rate was of interest. In 12 of 31 patients the cholesterol exceeded 200 mg. per 100 cc. when the basal metabolic rate was between plus 10 and plus 15 per cent, and in an additional 14 exceeded that value when the basal metabolic rate varied between plus 5 and plus 10 per cent. In other words, approximately 84 per cent of the patients showed somewhat elevated cholesterol values when the basal metabolic rate was between plus 5 and plus 15 per cent. The general clinical condition of the patient was always satisfactory with basal metabolic rates within such a range, and usually at its best when the metabolic rate was between plus 10 and plus 15.

Despite these facts, the absolute level of the blood cholesterol was hardly of as great importance as the percentage changes from the initial levels in each individual patient. This is readily shown in Fig. 4, which is a composite curve of the percentage changes in blood cholesterol plotted against the basal metabolic rates. In this curve the initial value for blood cholesterol in each individual patient is taken as 100 per cent, and subsequent values are figured as a percentage deviation therefrom. While there was a great deal of "scattering" of the figures here plotted, the mean values and standard deviation permit the conclusion that a straight line relationship apparently exists between the

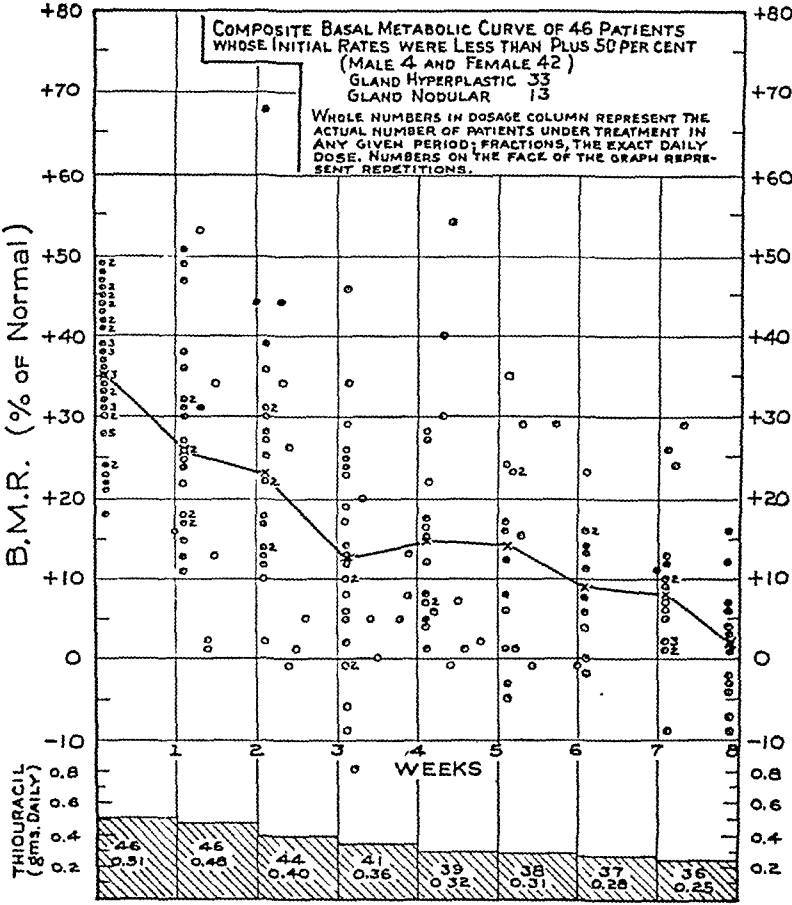
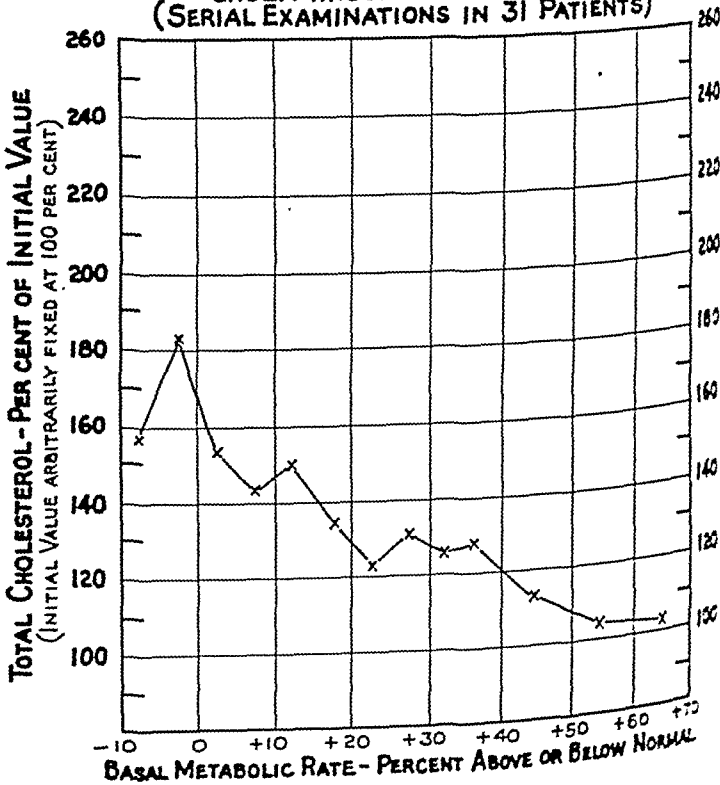


FIG. 3

PERCENTUAL CHANGES IN CHOLESTEROL IN RELATION  
TO ALTERATIONS IN THE BASAL METABOLIC RATES  
OF PATIENTS WITH THYROTOXICOSIS  
UNDER THIOURACIL TREATMENT  
(SERIAL EXAMINATIONS IN 31 PATIENTS)



percentage increase in the blood cholesterol and the decrease in the basal metabolic rate.

### *The blood picture*

In two patients, anemia in which the erythrocyte count was 3.5 million or less and the hemoglobin 65 per cent or less has been encountered after several months of treatment. One of these patients was relieved by the administration of iron by mouth while thiouracil was continued; in the other, thiouracil was stopped and an operation performed.

The behaviour of the leucocytes of patients under treatment with thiouracil is sum-

tients (Cases 22 and 34), and necessitated discontinuance of the drug. Both patients were seriously ill, but recovered completely in from 10 to 13 days, one following a series of transfusions and injections of pentnucleotide, and the other following a policy of watchful waiting during which fluids were forced to favor excretion of the drug. These are reported in detail elsewhere (39). The first of these had received approximately 21 gms. of drug at the rate of 0.5 gm. daily. She developed a sore throat and bleeding of the gums two days prior to the complete disappearance of the granulocytes.

The second patient had been on graded

TABLE 7. DATA FROM BLOOD COUNTS IN 78 PATIENTS WITH THYROTOXICOSIS UNDER TREATMENT WITH THIOURACIL

	Leukopenia ( $<5,000$ cells cu. mm.)			Relative granulocytopenia (Polys $<50\%$ )		
	No. cases	Week of appearance		No. cases	Week of appearance	
		Range	Average		Range	Average
Pretreatment	5	—	—	6	—	—
Appearing and Disappearing during Treatment	11	1 to 6	2.8	14	1 to 16	3.5
Reaction Necessitated stopping Drug	2	1.5 to 6	3.8	2	1.5 to 6	3.8

marized in Table 7. Leukopenia, that is, 5,000 or less leucocytes per cu mm. was encountered in the pretreatment period in 5 of 78 cases; none of these had a relative granulocytopenia; that is, less than 50 per cent polymorphonuclear leucocytes in the stained smear. However, there were six instances of relative granulocytopenia in which the total leucocyte count was normal. All of these abnormalities disappeared under treatment with thiouracil without any exacerbation of the initial or pretreatment disturbance.

On the other hand, 11 patients developed a leukopenia, and 14 a relative granulocytopenia, while undergoing treatment with thiouracil (Table 7). The majority of these reactions appeared between the second and third weeks of treatment with an over-all average for the former of 2.8 weeks and for the latter of 3.5 weeks. All of them disappeared without interfering in any way with the therapeutic regimen. Severe leukopenia with agranulocytosis occurred in two pa-

doses of the drug for two months, beginning with 0.6 gm. daily, and was receiving 0.2 gram daily at the time of the reaction. On the tenth day of treatment and on several subsequent occasions prior to the development of the agranulocytosis either leukopenia or abnormal white forms in the stained smears had been observed. In this patient the onset of fever and disappearance of granulocytes were simultaneous.

### C. Toxic reactions

#### *1. Those which disappeared without altering the course of therapy.*

Generalized pruritus occurred in five patients; rashes, most marked over the forearms and legs in three; edema, most marked about the eyes and around the ankles in three; diarrhea in one; and dryness of the mouth with excessive thirst, in one. Reference has already been made to leukopenia and granulocytopenia.

## 2. *Those which necessitated cessation of therapy*

Two patients with agranulocytosis have already been discussed. In two additional patients, the onset of a chill associated with high temperature, urticarial rashes, sore-throat and symptoms of "the grippe" necessitated the discontinuance of therapy. Each of these patients, whose reactions are detailed elsewhere (39), recovered completely in about ten days. In each, a subsequent single dose of the drug reproduced within six hours the entire syndrome in a somewhat milder form. The hypersensitive rather than the toxic nature of this type of reaction seems to be confirmed.

Myxedema has been observed in four patients, two of whom had hyperplastic and two had nodular goiters. Their lowest basal metabolic rates were minus 8, minus 12, minus 11, and minus 15 respectively. In one, the myxedematous state was complicated by cardiac failure, so that it is quite possible that her lowest recorded basal metabolic rate of minus 8 was considerably higher than was to be expected as a result of the thyroid status alone. All of these patients recovered spontaneously after cessation of the drug; restitution began at approximately five days and was completed within two weeks. It is easy to avoid myxedema by keeping the basal metabolic rate above plus 5. The state was purposely induced in three of the four patients above in order to study serial changes in capillary permeability. The fourth patient had failed to keep several appointments but had continued "the greater than maintenance dose" of the drug previously prescribed. In all of these four patients the drug was resumed at "maintenance" levels when the basal metabolic rates had returned to between plus 10 and plus 15 per cent.

### D. The influence of thiouracil on diabetes mellitus in the thyrotoxic patient

Eleven of our 78 thyrotoxic patients had a pre-existing diabetes mellitus; five of these were associated with a hyperplastic goiter and six with a nodular type. During the period of treatment with thiouracil the tolerance of one of these patients decreased as shown

by the need for a permanent increase in the dosage of protamine zinc insulin from 40 to 50 units daily. However, this change in tolerance occurred subsequent to an intercurrent pneumonic infection and was probably due to it. In three patients, there was no change in tolerance. All three were maintained on previously selected diets, had normal blood sugars at the beginning of therapy and did not show glycosuria before or during the period of treatment with thiouracil. One needed 30 units of protamine zinc insulin daily throughout the period of observation. The others were controlled with diet alone.

All of the remaining eight cases showed improvement in their diabetic status through the use of thiouracil. Six were without glycosuria on diet therapy without insulin but all had high fasting blood sugars when first seen; the actual figures in mg. per 100 cc. being 350, 280, 207, 201, 194, and 180 respectively. Serial weekly examinations showed a normal blood sugar as soon as the basal metabolic rates were brought within normal levels. The two remaining patients needed insulin to prevent glycosuria. Under treatment with thiouracil the amount of protamine zinc insulin required was reduced from 125 and 100 units respectively to 30 and 10 units respectively.

### E. The maintenance dose of thiouracil

Fifty-four patients were followed to complete control of their thyrotoxic state while under treatment with thiouracil. The maintenance doses as related to the initially observed basal metabolic rates are recorded in Table 8. The majority of patients—28 in all—were maintained satisfactorily on 0.2 gram of drug daily. However, the average daily dose for all patients with pretreatment basal metabolic rates of plus 30 or more was slightly higher (0.23 gm.) than that necessary for those whose initial rates were below plus 30 (0.17 gm.). The maintenance dose was determined by "trial and error." In 13 instances the dose had to be increased after gradual reduction, in order to prevent the recurrence of symptoms and signs of thyrotoxicosis; in five instances from 0.1 to 0.2 gm.; in ten

from 0.1 to 0.3 gm.; in four, from 0.2 to 0.3 gm., and in two, from 0.3 to 0.4 gm. It is therefore patent that cases must be individualized. The drug should not be abandoned as unsatisfactory because too small a maintenance dose is attempted.

#### The discontinuance of therapy

No patient was able to stop treatment until thiouracil had been continued for at least two months. If thiouracil was used less than two months, symptoms invariably returned (Table 2). At the end of two months, it was successfully stopped in five patients. However, attempts to discontinue therapy in some individuals after 15 months have led to an exacerbation of the disease process. Thus far, therefore, there is no "rule of thumb" by which the termination of treatment can be predicted. It is our present practice to reduce the dose of drug at first rapidly until a fairly stable non-toxic state has been attained. Further reduction is made much more gradually, beginning as a rule between the third and fourth months of treatment.

### III. DISCUSSION

Williams believes that probably more than 1000 patients with thyrotoxicosis have received thiouracil (61), although his remarks and conclusions are based upon 304 cases sufficiently studied by himself and others to permit satisfactory summation. Since his report was written, *i.e.* since July, 1944, at least 500 additional cases have been discussed in the literature, exclusive of those herein mentioned. It is difficult to make an accurate count as some of the cases have been mentioned by the same author or group of authors in more than one article. Moreover, there are undoubtedly more patients under treatment than have been summarized in the literature, as a number of authors have written only of their unusual experiences, or have only discussed cases bearing on some phase of the action of the drug which they have singled out for special study. It has been our effort to summarize the major clinical data on all our cases so that we may gain perspective on the over-all action of the drug as it

may be expected to affect large groups of people when applied in the general practice of medicine. With this in mind certain features in our results justify comment:

#### A. Toxic reactions

Agranulocytosis occurred in two of our 78 patients (2.5 per cent). These we have described elsewhere in detail (39). This is the

TABLE 8 DAILY MAINTENANCE DOSE OF THIOURACIL IN RELATION TO THE PRE-TREATMENT BASAL METABOLIC RATE

Initial B M R (% of normal)	No of patients	Daily dose of thiouracil (gm.)
+50 and over	2	0.4
	8	0.3
	12	0.2
	2	0.1
	Tot 24	Av 0.24
+30 to +50	2	0.4
	4	0.3
	10	0.2
	3	0.1
	Tot 19	Av 0.23
Up to +30	1	0.3
	6	0.2
	4	0.1
	Tot 11	Av 0.17

only serious complication to be encountered in the use of the drug. It has been reported in seven patients in addition to the two mentioned herein (1, 2, 17, 29, 35, 52, 60). Of these, three have died (17, 29, 35) as a result of the agranulocytic reaction. However, in one of these (29), the patient was 62 years old and was suffering from diabetic coma as well as the drug reaction when admitted to the hospital. Three additional cases have been described in the literature under the title of agranulocytosis in which there was actually only a neutropenia, and the symptoms were mild (34, 35, 44). It is quite likely that most of the patients who have developed an agranulocytosis have been reported not only because of the severity of the symptoms but also because, as is the case with every new drug, the physician's attention is immediately focussed upon any unusual or untoward aspect thereof. If that is the case then there

have been nine reactions in approximately 2500 reported cases, or an incidence of 0.36 per cent. Even if every series ran as high as our own, with an average of 2.5 per cent reactions of a severe nature, the morbidity and mortality is certainly less than that attendant upon previously recognized means for dealing with thyrotoxicosis. The fact remains nevertheless that agranulocytosis is an alarming manifestation of hypersensitivity or toxicity, and should make for caution in the use of the drug by all practitioners.

The majority of agranulocytic reactions have occurred between the third and seventh weeks of treatment. A factor in the production of the bone marrow block appears to be the tremendous concentration of the drug in the marrow as shown by Williams, Kay and Jandorf (63). Using human subjects, these workers showed that bone marrow concentrations of thiouracil rose rapidly following the administration of from 0.4 to 1.2 grams of thiouracil daily. Within three days the average bone marrow-blood ratio of the drug was 12, and in those patients treated from six to 22 days the average bone marrow-blood ratio rose to 85. This was the highest concentration of the drug in any tissue of the body. In the patients observed for longer periods of time the thyroid showed the second greatest concentration with a tissue-blood ratio of 46 to 1, that is only slightly more than half that observed for the bone marrow (85 to 1). If possible a successful substitute for thiouracil should have less tendency to pack the bone marrow and even greater proclivity for the thyroid.

One other type of toxic reaction justifies emphasis. We have had two cases in which there occurred chills, fever, and widespread urticarial rashes. Neither in our cases nor in those reported in the literature has this type of untoward response endangered the life of the individual, but in many instances, as in both of our patients, it has been sufficiently severe to warrant cessation of the drug. It appears to be a true hypersensitivity, and has usually occurred before the tenth day of administration of the drug. In many instances, as in both the cases above reported, attempts

to reintroduce the drug, even in small quantities, have usually resulted in a reproduction of the symptoms. Desensitization has been attempted by some workers (1-3), but the degree of success is questionable.

#### B. The uniformity with which all types of thyrotoxicosis may be relieved

If thiouracil is continued a sufficiently long time in sufficiently large dosage it has been our own experience as well as that of the majority of workers that thyrotoxicosis, whether due to a diffusely hyperplastic or nodular gland can be completely relieved. In one of our patients (*Case 21*), it was seven weeks before a basal metabolic rate within normal range could be attained, although 0.8 gm. of drug were given for one week and 0.6 gm. for three additional weeks, and 0.6 gm. for the remainder of the seven week period.

Paschkis and his associates also called attention to the necessity for very large doses in one patient who required 2.0 gm. of the drug daily for a short time (46). Rose and McConnell (51) treated one patient for 34 weeks before her basal metabolic rate fell below plus 15 per cent.

As a rule some symptoms are improved early as the seventh to tenth day, and the average patient is well on the way to complete control by the end of the third week. Some failures have been reported in the literature (22, 49, 51, 57-discussion by Ellis, 5) but in every instance one can say with certainty that the dosage of the drug was too small, the period of trial too short, or previous medication, particularly iodine, not properly evaluated; and so forth. Rose and McConnell (51) have called attention to these factors and some length in discussing their own so-called failures. It seems therefore safe to say that any type of thyrotoxicosis may be relieved by the drug provided proper conditions of treatment are observed.

#### C. Criteria for optimum treatment

The fact that we have been able to produce the picture of both simple hypothyroidism and myxedema by high dosage of thiouracil

our patients (Cases 17, 29, 52, and 64) justify some comment on ways and means of maintaining the patient in an optimal state. Limsworth (22) sharply distinguishes these "true toxic effects" of the drug from the ferile and hematopoietic or "hypersensitive reactions." In avoiding over-dosage, attention to the following have been of value to us:

#### *The basal metabolic rate*

As soon as a basal metabolic rate of plus 5 or below has been attained, we have striven to ascertain immediately the lowest maintenance dose which will keep it between plus 5 and plus 15. It is in this range of basal metabolism that patients have been most consistently free of subjective symptoms, have achieved normal pulse rates and blood pressures, and have established satisfactory increments of weight.

#### *The blood cholesterol*

When a formerly normal or low normal cholesterol rises above the top normal figure (200 mg. per 100 cc.) the dose of drug may be reduced irrespective of the concomitantly recorded basal metabolic rate. Blood cholesterol levels between 175 and 250 mg. per 100 cc. are common in the adequately treated patient.

#### *Enlargement of the thyroid gland*

When enlargement of the thyroid gland occurs, it usually implies the formation of a colloid poor in iodine with a beginning exhaustion of the highly overstimulated thyroid cell. While the decreasing basal metabolic rate and the rising blood cholesterol usually give us warning that this is occurring before the gland actually enlarges, nevertheless there have been several instances in which the enlargement of the gland appeared so rapidly that the other signs had been overlooked. This increase in the thyroid may occur at any time but has usually appeared between the second and sixth months of treatment. Discontinuance of the drug or a reduction in the size of the dose has always been attended by a recession in the thyroid. If on a second occasion cellular exhaustion is produced, the

gland responds in a manner similar to that previously observed.

#### D. The significance of a decrease in the size of the thyroid gland

We have just discussed the probable cause of the enlargement of the thyroid which occurs when treatment with thiouracil is being pushed too far. There remains to be considered the transient decrease in the size of the gland which is most frequently observed between the second and fourth weeks. While we have performed no biopsies, it is our belief that this transient decrease in size corresponds to the time at which the gland is yielding to the tissues the excessive amounts of thyroglobulin present prior to the beginning of treatment. This concept would be in accord with the findings noted in thyroids removed at operation (3, 4, 10, 42, 51, 60).

#### E. The duration of treatment

Our ability to discontinue the drug in the average patient without a recurrence of symptoms has varied widely . . . from 2.5 to 16 months. This seems to have been the universal experience of all observers. The results of several serve to stress the fact (1-4, 6, 7, 44, 46, 51, 60-62) There is evidence to suggest that the drug can not be successfully discontinued until such time as the thyroid cell has reached an "exhaustion" or "near-exhaustion" stage, or until the excessive hypothalamic-pituitary stimuli have been reduced. Because of the large number of variables implied in the two statements of the above sentence, it is rather obvious that the duration of successful treatment becomes a distinctly individualistic matter.

Unsuccessful attempt has been made on three occasions to stop treatment in one of our patients (Case 29) who has been taking thiouracil for 16 months. Abnormal business stresses leading to long hours of work, excessive stimulation with alcohol and coffee, and an initially asthenic constitution seem to be the contributing factors in maintaining his pituitary and thyroid activity at a high level. Another patient of rather mercurial disposition (Case 41) has slipped into and out of



hypothyroidism on more than one occasion, although her condition has been continuously watched at not longer than monthly intervals. Therefore, for the present at least, we can not establish a hard-and-fast rule for stopping therapy. This raises the whole problem of how long we should use thiouracil before resorting to some other form of therapy, such as surgery. Our experience affords no scientific answer to this question. Perhaps work of the type already begun by Williams and his associates (63) may throw light upon it. It would certainly be invaluable to know tissue concentrations of the drug after it had been used for months. Do the tissues establish a level varying with the dose of drug used? Can this level be maintained indefinitely without damaging the tissues of the host? The answers to these and similar questions are essential to a full evaluation of the place of thiouracil in the treatment of the thyrotoxic patient.

#### IV. SUMMARY

1. Ten male and 68 female patients with thyrotoxicosis have been studied while under treatment with thiouracil.

2. Of these 78 patients, 53 had a diffusely hyperplastic and 25, a nodular type of goiter.

3. Periods of treatment have varied from two weeks to 16 months.

4. "Nervousness," apprehension, palpitation, and loss of weight were the most common symptoms and were among the first to disappear.

5. Exophthalmos was present in 38 of the 78 patients, and was decreased under treatment in 17 instances.

6. In 65 instances, the thyroid was initially enlarged. Under treatment there was a transient decrease in size in 20, and a more prolonged increase in size in 21.

7. The auricular fibrillation initially present in 18 individuals disappeared in 12 without other therapy than the thiouracil.

8. Eight of the 78 patients were continued on the drug only sufficiently long to prepare them for surgery.

9. The basal metabolic rate was depressed by thiouracil in both the nodular and hyper-

plastic types of thyrotoxicosis. The average initial basal metabolic rate for the entire group was plus 46.0 per cent with a low plus 18 and a high of plus 87. The approximate time taken for the basal metabolic rate to reach plus 15 or below was three weeks.

10. The initial blood cholesterol level was above 200 mg. per 100 cc. in 11 patients. The pretreatment blood level for this substance bore no direct relationship to the height of the basal metabolic rate nor to the severity of the thyrotoxic state. In every instance, the basal metabolic rate fell, the blood cholesterol rose.

11. Toxic reactions included two cases of agranulocytosis and two cases with severe febrile reactions, chills and urticarial skin lesions.

12. Eleven of the 78 patients had a pre-existing diabetes. In three of these 11 patients there was no change in glucose tolerance under treatment.

13. The maintenance dose of thiouracil varied from 0.1 gm. to 0.4 gm. daily with an average of 0.23 gm. daily for the 67 patients whose initial basal metabolic rates were plus 30 or above.

14. The treatment of 14 patients was successfully discontinued, as follows: at the end of two and a half months in five cases; five months in one; five months in one; six months in two; seven months in two; and eight months in three.

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# Thiouracil in the Control of Thyrotoxicosis

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THE rapid accumulation of a relatively large amount of encouraging data pertaining to the therapeutic use of thiouracil suggests that this or some similar compound eventually may attain recognition for the medical treatment of patients with thyrotoxicosis.

The experimental background leading to the development of this form of therapy, as well as the results of its rather extensive clinical trial, have been reviewed by Astwood (1), Williams (14) and others (2, 10, 12, 18). Although the exact scope of the value of thiouracil has not been determined as yet, recent editorial comment (4) intimated that a safe basis seemed to have been established or continued observations concerning its therapeutic action. In conformity with this opinion, the following experiences with the drug are presented.

## THE INVESTIGATION

The present report is based upon observations made on 35 unselected thyrotoxic patients who were treated with thiouracil. Nine of these patients were referred to in a previous preliminary communication on the same subject (18). The whole series comprised 30 females and five males ranging in age from 13 to 65 years; the majority, however, were between the ages of 20 and 50 years. On the basis of the clinical diagnoses, there were 19 cases of exophthalmic goiter (Graves' disease), 11 cases of diffuse (non-exophthalmic) toxic goiter and five cases of toxic nodular goiter. Four were examples of recurrent hyperthyroidism following thyroidectomy.

One patient was in the sixth month of pregnancy at the time the treatment was started. Another had a thyrotoxic psychosis with extreme agitation. Twenty-five of these patients were under observation in the hospital during the initial stage of their thiouracil therapy; the remainder were followed entirely as out-patients. In the majority of instances, the pre-treatment levels of the basal metabolic rate, the resting pulse rate, the blood chemical constituents, etc., were established by observations on at least two consecutive days. Following the institution of treatment with thiouracil, attention was focussed upon the clinical status of the patient with special reference to any apparent changes in the thyrotoxic manifestations and in the size and consistency of the thyroid gland. Estimations of the B.M.R. and of the concentrations of cholesterol (total) by the method of Myers and Wardell (9) and of the alcohol-insoluble (organic) iodine<sup>1</sup> in the whole blood were performed at weekly intervals and, when possible, leukocyte counts were made twice weekly for the first month. Thereafter, the interval between the tests was lengthened depending upon the therapeutic response or other circumstances.

The initial dosage of thiouracil<sup>2</sup> was 600 milligrams daily given as three doses of 200 milligrams each at approximately six-hourly intervals. With the occurrence of obvious im-

<sup>1</sup> The estimation of iodine in the residue obtained after treating oxalated whole blood with absolute ethyl alcohol was performed by means of a method described by Perkin (11) with certain technical modifications (16, 17)

<sup>2</sup> Supplied by the Lederle Laboratories, Pearl River, New York, courtesy of Dr Stanton M. Hardy

provement as indicated by a decline of the B.M.R., usually after one or two weeks, the dose was reduced to 500 or 400 milligrams per day. Subsequent reduction followed until,

months, 2 cases; from 6 to 9 months, 5 from 3 to 6 months, 15 cases; less than 3 months, 7 cases.

## RESULTS

In view of the many variables involved in so-called toxic thyroid disease, a clear picture of the results attainable by this method of treatment is not easy to present.

*General Considerations.* An improvement of the subjective symptoms is especially difficult to assess quantitatively. However, relief from the disturbances commonly associated with the hyperthyroid state, such as apprehension, irritability, restlessness, nervousness, or palpitation, muscular weakness, the phobia, sweating, vasomotor instability, diarrhoea, is indicative of the usefulness of the drug.

Speaking generally, the results of the treatment with thiouracil in this group of patients may be graded as follows: excellent in 15 cases; good in 10, fairly good in 5 and poor in 5. It is only fair to state that the poor results may have been influenced by certain factors such as failure of cooperation on the part of the patient, lack of adequate data, the previous use of iodine medication and, in one instance, the development of an idiosyncrasy to the drug. On the whole, the response was more satisfactory in the younger patients than in the older ones. Although both the diffusely hyperplastic and the adenomatous goiters responded favorably to the drug, symptomatic improvement was more striking in the former. The results were highly satisfactory in the cases of post-operative recurrence of hyperthyroidism. The pregnant patient continued to take thiouracil up to following parturition without apparent effect to herself or the child. The psychotic patient regained an essentially normal mentality.

The changes in the objective manifestations of toxic thyroid disease, on the other hand, lend themselves to quantitative appraisal. Included in this category are basal metabolic rate, the pulse rate, variations in body weight, the blood cholesterol concentration and the organic

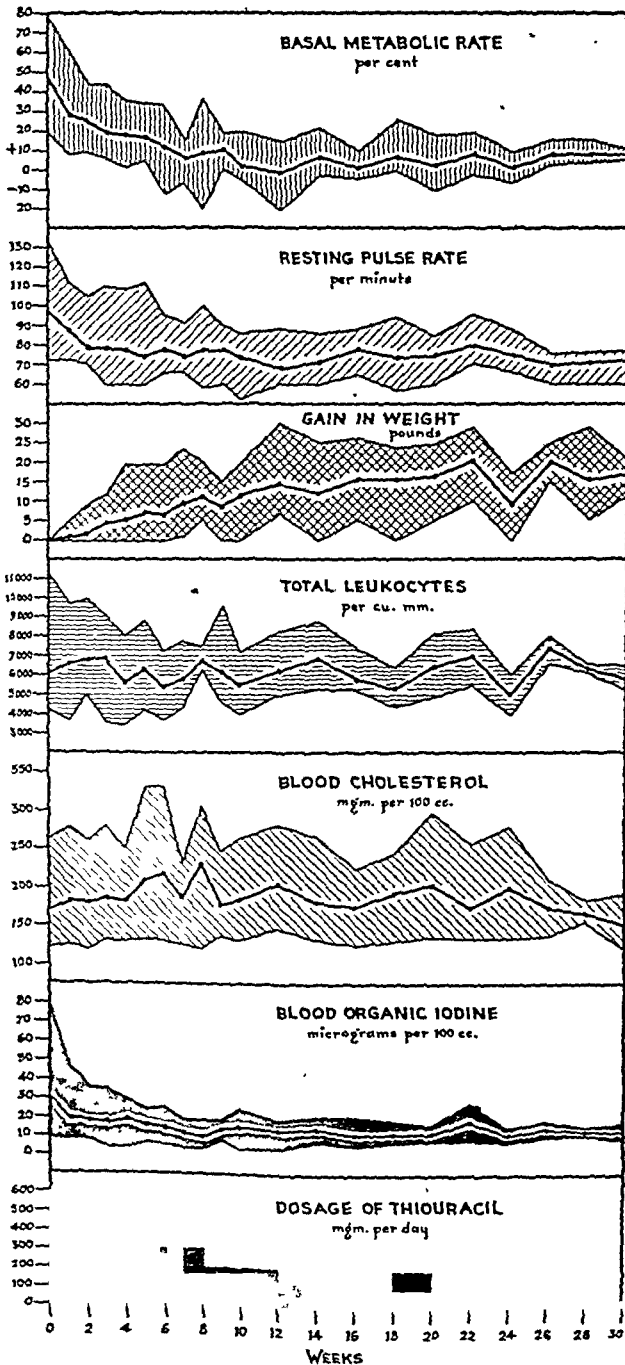


FIG. 1. The effects of thiouracil in the treatment of 30 patients with thyrotoxicosis.

after four or six weeks, a maintenance dose of 100 milligrams or less per day was established. The duration of the treatment of the patients included in this study has been as follows: 12 months or longer, 6 cases; from 9 to 12

content of the blood. Data pertaining to these features in the 30 responsive cases are shown in Figure 1. The extreme values for the several items at various times up to 30 weeks are depicted along with curves representing the mean values.

*The Basal Metabolic Rate.* In all the patients but two in the group under consideration, there was a prompt decline of the basal metabolic rate, in some instances to subnormal levels. The length of time required for the B.M.R. to reach +15 per cent or lower varied from two to eight weeks with a general average of about six weeks. There did not appear to be any definite relationship between the degree of thyrotoxicosis and the speed with which the B.M.R. returned to normal. The return was faster, however, in the younger patients than in the elderly ones and delayed in those who had received iodine medication previously. Minor elevations of the B.M.R. during the course of the treatment may have been related in some cases to too rapid decrease of the dosage of thiouracil.

*The Resting Pulse Rate.* In every instance the resting pulse rate decreased. Furthermore, in several patients with cardiac irregularity, the rhythm returned to normal both with or without therapy other than the thiouracil.

*Gain of Weight.* The body weight of 26 of the 30 patients increased during the treatment. The gain of weight was not pronounced during the first two or three weeks, but thereafter the majority of the patients showed a gradual increase in weight and in some cases it became excessive.

*The Blood Cholesterol.* As has been found by some observers (2, 14), patients who respond to thiouracil may exhibit an increase in the total cholesterol content of the blood sometimes to quite high levels. Such findings have been questioned by others (3). A rise in the cholesterol value occurred in 26 of the patients investigated. No elevation took place in three cases and in one the study was omitted. The rise of the blood cholesterol seemed to correspond, more or less, with the initial drop of the B.M.R. and, in most of the

cases, after several weeks the cholesterol concentration tended to level off at an approximately normal figure.

*The Blood Organic Iodine.* The so-called organic blood iodine is regarded by some investigators as an index of the amount of thyroid hormone produced (15). The normal value for the alcohol-insoluble (organic) iodine estimated by the method employed in this laboratory is from 8 to 12 micrograms per 100 cc. of whole blood. A systematic study of this organic blood iodine was made in 28 of the patients. The pre-treatment values in different cases varied from slightly above normal to 76  $\mu$ g. per 100 cc. of whole blood. The majority, however, were definitely high, with a general average of 30  $\mu$ g. The administration of thiouracil brought about a fairly prompt decline of the blood iodine in 21 of the patients, indicating that the amount of thyroid secretion poured into the blood stream was reduced. There was a less pronounced change in seven cases.

*The Total Leukocytes.* In view of the reputed tendency of thiouracil to cause leukopenia in a relatively small percentage of persons receiving the drug, periodic total leukocyte counts were performed on all 30 patients. In only 6 were counts recorded below 5000 cells per cu. mm. Only 2 of these counts were below 4000 per cu. mm. A reduction of the dosage of thiouracil resulted in a prompt rise of the leukocytes to the normal level.

*Gross Changes in the Thyroid Gland.* The term "chemical thyroidectomy" as applied by Harrington (5) to the clinical effects of thiouracil is apt in most respects but not, of course, with respect to the ablation of an existing goiter. Regular records of the size of the gland were made in 22 cases in this series by means of measurements of the circumference of the neck. An increase of size was registered in 16 cases and no change was observed in six. Allowing for inaccuracies inherent in this method of estimating changes in the size of the thyroid gland, the observations indicated that in a majority of the cases the gland actually enlarged during thiouracil therapy. The degree of enlargement thus measured, varied from  $\frac{1}{4}$  inch to 1 inch, with

an average of  $\frac{5}{8}$  inch; an increase which is, perhaps, relatively insignificant considering that a general increase of the body weight occurred also. Two patients elected operation because of the development of pressure symptoms. The glands did, however, tend to become softer and usually the thrill and bruit disappeared. A return to the initial dimensions was noted in several cases during the stage of maintenance treatment.

*The Exophthalmos.* Of the 19 patients with exophthalmos, a decrease of the proptosis was noted in 12 during the treatment, judged on the basis of inspection only. The degree of exophthalmos was apparently unchanged in 7 cases. It is noteworthy that the regression of this manifestation of the thyrotoxic state succeeded, in some instances by several months, the improvement of the other major symptoms.

*Sustained Remissions.* It has been claimed by Astwood (1) that the treatment of patients for six to eight months with thiouracil in dosages that maintain a normal or somewhat subnormal basal metabolic rate may initiate spontaneous lasting remissions of the thyrotoxicosis. The administration of thiouracil was stopped, or at least diminished almost to the vanishing point, in six of the patients in the present series after they had been receiving the drug for periods ranging from five to nine months, at which times the thyrotoxic manifestations were in abeyance. In one patient symptoms of thyrotoxicosis and hypermetabolism recurred within two months following the cessation of the treatment. The other patients maintained their remissions, some for as long as six months without the drug. Minor relapses could be induced by physical or emotional stress. Certain patients were reluctant or actually refused to discontinue the use of thiouracil for fear of a recurrence of the thyrotoxic symptoms.

*Unresponsiveness.* As has been mentioned by Astwood (1), there are two types of patients in particular who do not respond promptly to thiouracil therapy. These are: (1) Those who have been treated with iodine previously and (2) patients with longstanding toxic nodular goiters wherein is

stored a large amount of hormone-bearing colloid. Examples of both of these types of cases were encountered in the present series.

In Figure 2 is shown a comparison of the therapeutic response to thiouracil of a patient who had been treated previously with iodine doses of Lugol's solution and one who had not been so treated. In the former case there was actually a rise of the B.M.R. following the cessation of the iodine medication and during the early stage of thiouracil therapy. The consensus is, however, that if the treatment is persisted, the desired result, as in this case, will follow.

*Toxic Reactions.* The main disadvantage of thiouracil as a therapeutic agent seems to be its unpredictable tendency to produce toxic reactions of various kinds which, as stated by Williams (14), occur in 10 per cent of cases. The most serious event of this sort is leukopenia and agranulocytosis, an occasional fatality due to the latter condition having been recorded (6, 7). It is noteworthy that in several of the published reports of leukopenia and granulocytopenia associated with the use of thiouracil (8, 13), the dosages were relatively large and sustained. Such complications present a definite handicap to the general therapeutic application of the drug.

One patient in this series responded unfavorably owing to the development of an idiosyncrasy to thiouracil. This was the case of a non-atopic woman, aged 56, with chronic hyperthyroidism. The B.M.R. on two occasions was +41% and +35%. Three days following the institution of treatment with 600 milligrams of thiouracil daily, she complained of headache, insomnia and general malaise. Her apprehension increased, the heart beat became faster and somewhat irregular. There was discomfort in the chest, nausea and occasional vomiting. The temperature gradually rose from normal to 102°F., but there was no sore throat or other evidence of inflammation and no change in the leukocytes. Following cessation of the treatment, the temperature promptly returned to the normal level and the distressable symptoms disappeared. Four days later as a trial, the patient was given 200 mg.

ums of thiouracil as a single dose. Shortly thereafter she experienced a sharp pain in the epigastrium and a pounding sensation in the head. Her face became flushed, the con-

as rapidly as they had risen and within 24 hours all of the untoward manifestations had disappeared. The total leukocytes had increased to 4,800 per cu. mm. with 70 per cent

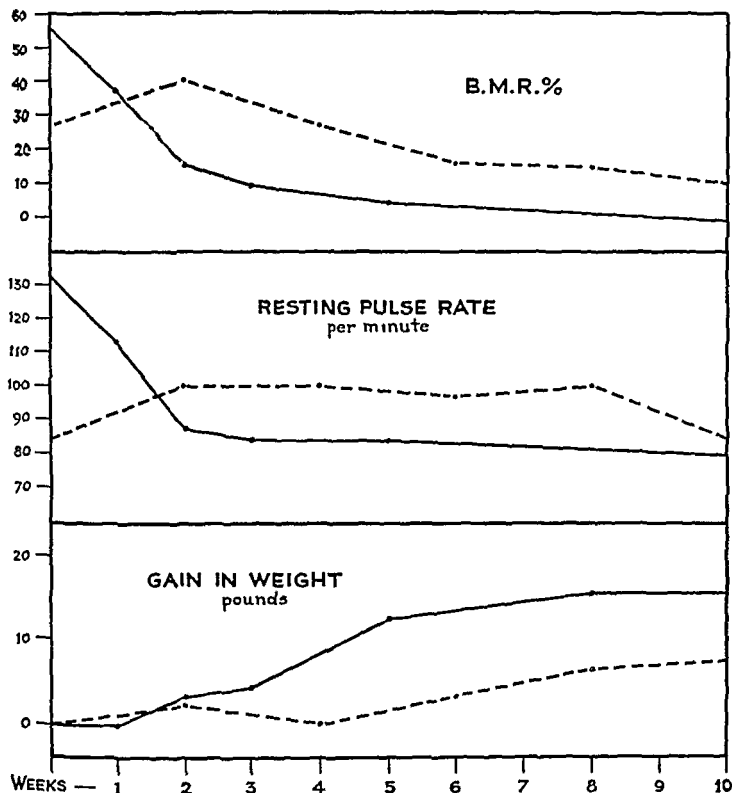


Fig 2 A comparison of the effects of thiouracil in the treatment of (1) A thyrotoxic patient who had received no previous iodine medication—solid lines and (2) A thyrotoxic patient who had received previous iodine medication—broken lines

neutrophils were congested and her eyes were red. There was circumoral pallor. She had chill and vomited. The temperature rose suddenly to 104.8°F, the pulse rate increased from 80 to 140 per minute and the total leukocytes were 2,400 per cu. mm., 80 per cent of which were neutrophils. The temperature and the pulse rate dropped almost

neutrophils. Further treatment of this patient with thiouracil has not been attempted.

#### SUMMARY

In 30 out of 35 patients with thyrotoxicosis treated with thiouracil for periods of two to 16 months, the results were favorable as indicated by a relief of the thyrotoxic symp-



toms, an increase of body weight and blood cholesterol and a reduction of the organic iodine of the blood. Thiouracil did not alter the size of the thyroid gland or consistently affect the degree of exophthalmos. One patient developed a severe febrile reaction and leukopenia.

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# Prolonged Administration of Diethylstilbestrol<sup>1</sup>

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DIETHYLSTILBESTROL in the few years since its introduction has become recognized as a highly effective estrogenic agent for the treatment of a variety of gynecological disorders. In view of the fact that it rather frequently gives rise to nausea and vomiting it was designated by some as "the vomit drug." Despite the failure of several investigations to demonstrate significantly harmful effects of the drug when used within appropriate levels of dosage, its ill repute has persisted.

In December, 1939, we reported our first observations on the so called toxic effect of diethylstilbestrol. The results of the investigation were published in 1941 (1). These results encouraged us to continue its use and to date we have given diethylstilbestrol to 27 patients. Varied tests were conducted before, during and following the prolonged administration of diethylstilbestrol. None of these laboratory data yielded evidence to suggest that chronic toxicity or a neoplastic transformation occurs as the result of the therapy. As the evidence accumulated on the relative harmlessness of the drug, we felt justified in deliberately exploring the effects of high dosage of this material. One representative series of studies, of Case M M, is summarized in Table 1.

Some aspects of the study may be separately considered. There were 86 cases of vulvovaginitis in children of from two to twelve years of age who received from 1.0 to 5.0 mg diethylstilbestrol daily. In addition, eight

girls, ranging in ages from two to eight years received from 10.0 to 25.0 mg of diethylstilbestrol daily or every second day for periods of from one to eight months. In this series control tests were made once each month. In addition, roentgenograms of the hands and forearms were made once every 30 or 60 days. In another series of normal children of the same ages, roentgenograms were taken before, during and following the administration of diethylstilbestrol. In this and in the control series no significant changes in ossification were disclosed. In this series the laboratory tests also failed to demonstrate any abnormal conditions.

In a selected cumulative series of 136 women, given diethylstilbestrol for one or another gynecological condition, the dose was gradually increased from 1.0 mg to 5.0 mg by mouth every three to seven days until some were taking 100.0 mg each a day. Furthermore, they were going to the Endocrine Injection Clinic where they received intramuscularly, once or twice weekly, doses of from 25.0 to 250.0 mg of diethylstilbestrol incorporated in olive oil in a concentration of 25.0 mg per cc. One third of these patients were started on their diethylstilbestrol in the clinic, where they received smaller doses. They were admitted to the hospital in order that they might be studied more closely, and then large doses were given. This group demonstrated that, regardless of the amounts administered, there was no obvious harm to the patients. They were then dismissed to the clinic where they were continued on the doses of 100 mg per day with additional intramuscular injections of from 50 to 100

<sup>1</sup> Permission to do this research granted by the Research Committee of the Jefferson Davis Hospital

mg. two to six times weekly. A complete blood count and a urine analysis were performed two to three times weekly. In none of these cases was it possible to demonstrate by these tests any abnormal findings resulting from diethylstilbestrol therapy.

One woman, aged 38, died as the result of an auto accident while she was taking daily treatment of 5.0 milligrams of diethylstilbestrol; she had received a total of 250 milligrams. The pathologists were unable to discover any sign of gross or microscopic evidence of damage to the liver or to any other organ of the body as the result of the stilbestrol therapy.

Two patients, each about three months pregnant, were under observation because of threatened abortion. Each patient was given 950.0 milligrams of diethylstilbestrol weekly for an average period of 19 weeks, a total of

18,000 milligrams of diethylstilbestrol. During the latter part of the fifth month 2 mothers aborted live babies. Both babies died within several days. Each baby was autopsied. The parenchymatous organs were carefully studied grossly and microscopically and the pathologists could demonstrate significant changes from the normal.

A third series of studies were carried out on thirty-one normally pregnant women. Each received 100.0 milligrams of diethylstilbestrol daily, from the third month of pregnancy term, a total of 18,000 milligrams for each. The 31 babies born were normal. All babies exhibited a darkening of the areolae around their nipples, labia, and linea alba, similar in intensity to that of their mothers, indicating that this effect of diethylstilbestrol also is shared by the fetus. The diethylstilbestrol in daily doses of 100.0 milligrams

TABLE 1. PROTOCOL OF TESTS MADE ON M.M., A negro girl, fourteen years of age. The study began July 9, 1955. The patient had profuse hemorrhage when first seen. Amount of diethylstilbestrol administered (mg. per dose)

Month	Consecutive weeks	Orally	Intra-muscularly	Total dose	Data
1	1	8.0	80.0	88.0	First menses in her life began as profuse flooding. This episode of flooding stopped after 75 mg. had been given.
	2	11.5	6.0	17.5	
	3	17.5	2.0	19.5	
	4	18.5		18.5	
				143.5	
2	5	7.0	7.0	14.0	
	6	7.0	7.0	14.0	
	7	8.5	8.5	17.0	
	8	17.5	17.5	35.0	
				80.0	
3	9	20.0	20.0	40.0	Six days of bleeding. Spotted 6 days this week.
	10	65.0	65.0	120.0	
	11	70.0	70.0	140.0	
	12	55.0	55.0	110.0	
				410.0	Seven days bleeding.
4	13	55.0	80.0	135.0	Spotted on 7th day. Spotted on 6th and 7th days.
	14	35.0	35.0	70.0	
	15	35.0	35.0	70.0	
	16	35.0	35.0	70.0	
				345.0	
5	17	35.0		35.0	Spotted past 3 days.
	18	35.0		35.0	
	19	35.0		35.0	
	20	35.0		35.0	
				140.0	

TABLE 1—Continued

Month	Consecutive weeks	Orally	Intra muscularly	Total dose	Data
6	21	35 0		35 0	Bled first 6 days
	22	35 0		35 0	
	23	35 0		35 0	
	24	35 0		35 0	
				140 0	
7	25	50 0		50 0	Spotted last 4 days
	26	40 0		40 0	
	27	45 0		45 0	
	28	70 0		70 0	
				205 0	
8	29	70 0		70 0	
	30	85 0		85 0	
	31	105 0		105 0	
	32	105 0		105 0	
				365 0	
9	33	105 0		105 0	Menstrual flow normal 4 days
	34	105 0		105 0	
	35	105 0		105 0	
	36	105 0		105 0	
				420 0	
10	37	105 0		105 0	No flow this month
	38	105 0		105 0	
	39	105 0		105 0	
	40	105 0		105 0	
				420 0	
11	41	105 0		105 0	No flow
	42	105 0		105 0	
	43	105 0		105 0	
	44	105 0		105 0	
				420 0	
12	45	315 0		315 0	No nausea or vomiting
	46	700 0		700 0	No flow in 3 months
	47	700 0		700 0	Has attack of lower abdominal pain
	48	700 0		700 0	No nausea or vomiting in 2 months
				2,415 0	
13	49	700 0		700 0	No flow
	50	700 0		700 0	
	51	700 0	200 0	900 0	
	52	700 0		700 0	
				3,000 0	
14	53	700 0	1,250 0	1,950 0	No flow
	54	700 0	3,500 0	4,200 0	
	55	700 0	500 0	1,200 0	
	56	700 0		700 0	
				8,050 0	
15	57	400 0	1,000 0	1,400 0	

Study ended Sept. 5, 1940

The patient had 17,783.5 mg stilbestrol without significant changes in the laboratory findings

*Laboratory findings of Case M.M.*

## Blood examinations:

Date	Hb % (T)	R.B.C.	W.B.C.	Neut. %	Lymph. %	Eo. %	Mono. %
7-20-39	50	2.9	6.7	66	30	1	3
8- 3-39	59	3.5	5.4	66	34		
8-22-39	58	2.9	5.2	74	26		
9-13-39	66	3.4	10.2	78	18	3	1
10-11-39	70	3.8	7.7	68	20	3	9
10-21-39	84	4.0	7.8	65	35		
11- 5-39	66	3.6	8.2	72	23	4	1
12-23-39	68	3.3	7.0	58	36	2	4
1- 6-40	72	4.0	9.4	80	16	2	2
2-17-40	64	3.3	6.7	69	28	1	2
3- 2-40	62	3.2	6.8	64	34	2	
3-30-40	79	3.9	6.2	77	20	3	
4-13-40	77	3.5	6.2	64	46	6	3
5- 4-40	67	3.6	6.5	45	30	2	4
6- 1-40	82	3.6	5.4	60	36	2	2
6-29-40	68	4.1	6.4	62	36	2	
7-29-40	71	3.4	9.2	78	18	2	2
7-31-40	71	3.7	15.0	72	22	2	2
8- 2-40	77	3.7	9.9	74	26	2	
8-12-40	66	3.6	9.0	63	34	1	2
8-26-40	71	3.9	8.5	70	26	2	2
8-31-40	73	4.2	6.6	69	28	2	1
9-11-40	81	3.9	8.6	71	27		2
9-14-40			6.8	68	29		3

Sedimentation rate mm.  
per hour

Date	Result
8- 9-30	18.5
8-22-39	25.0
9-13-39	26.0
10-11-39	12.0
10-21-39	22.0
12- 9-39	13.0
12-23-39	20.0
1-27-40	30.0
2-17-40	28.0
3- 2-40	20.0
3-30-40	24.5
4-13-40	24.0
5- 4-40	19.0
7-15-40	31.5
7-29-40	34.0
8-12-40	35.0
8-26-40	24.0
9-11-40	20.0

Blood serum glucose  
(mg.%)

Date	Result
3-30-40	84.5
4-13-40	83.5
5- 4-40	88.8
6-29-40	111.5
7-15-40	89.0
7-29-40	79.5
8-12-40	68.1
8-26-40	69.2
9-11-40	75.2

Blood serum cholesterol  
values (mg.%)

Date	Result
11-17-39	200
4-15-40	236
5- 4-40	271
7-15-40	255
7-29-40	171
8-13-40	173
8-27-40	188
9-13-40	210

Blood serum sodium  
chloride values, mg.%

Date	Result
8-22-39	485
1- 6-40	492
1-27-40	487
3- 2-40	430
2-17-40	495
3-30-40	472
6-29-40	491
7-15-40	467
7-29-40	475
8-12-40	462
8-26-40	515
9-11-40	484

Serum non-protein nitrogen  
values (mg. per 100 cc.)

Date	Result
10-14-39	36.7
10-21-39	28.0
1- 6-40	26.8
1-27-40	30.0
2-17-40	23.8
3- 2-40	31.8
3-30-40	30.0
6- 1-40	34.4
6-29-40	34.6
7-15-40	33.0
7-29-40	23.0
8-12-40	29.0
8-26-40	21.6
9-11-40	31.0

## Icterus index:

Date	Result
12-23-39	4
1- 6-40	4
1-27-40	4
2-17-40	3
3- 2-40	3
7-15-40	3
7-29-40	3
3-30-40	7
8-13-40	4
8-27-40	5
9-13-40	5

## Urine examinations:

Date	How	Findings
7-22-39	Catheter	Normal
11-15-39	Catheter	1-5 w.b.c. per h.p.f.
6- 1-40	Voided	1-5 w.b.c. per h.p.f.
7-29-40	Voided	5-8 w.b.c. per h.p.f. Tr. of albumin.
7-31-40	Voided	150-200 w.b.c. per h.p.f. Tr. of albumin
8-31-40	Voided	Normal

Blood serum creatinine  
values (mg. per 100 cc.)

Date	Result
6-29-40	1.5
7-15-40	1.4

## Endometrial biopsy report:

11-15-39 Endometrium in resting stage with marked dilatation of glands.

## Serology:

Date	Report	
11-17-39	Kolmer negative	Kline negative
12-28-39	Kolmer anticomplementary	Kline negative
6- 1-40	Kolmer negative	Kline negative

## Roentgen examinations:

Date	Report
1-25-40	Epiphyses show no change.
7-10-40	Hands and forearms normal for bone conditions.
8-21-40	Long bones show no changes attributable to diethylstilbestrol.

2-19-44 This patient is near term. Her obstetrical history and physical findings have been normal throughout the pregnancy.

3-13-44 Normal male infant delivered.

## Findings on M M after delivery

Date	Hb%	R B C	W B C	Neut	Lymph	Lo	Mono	Sed rate
5 4-44	68	3 6	4 4	51	42	5	2	27 0 mm
5 20-44	60	3 6	5 5	61	39			18 0 mm
7 31-44	64	3 3	6 0	48	49	1	2	24 0 mm
9 23-44	80	4 1	5 1	52	39	5	4	18 0 mm

## Urine findings

Date	How obtained	Sugar	Albumin	Epith	W B C
9 30-44	voided	None	Trace	pos 1	50-60
10 14-44	voided	None	None	pos 3	None

## Vaginal smears

Date	Epi	Pus	Mono	Tri	G C	Staph	Strep	B coli	pH
4 26-44	None	None	None	None	None	Pos 3	None	Pos 2	6 0
8 19-44	Blood	Wassermann	negative						

## Tissue Examinations

Date	Tissue	Findings
4-26-44	Endometrial	Resting—6 weeks post partum
4 27-44	Culture for Monilia	negative
5 1-44	Endometrial	Late proliferative

to provoke any of the usual unfavorable effects in these pregnant patients.

Ten of these patients were each given 500 milligrams as a single intramuscular dose. All became nauseated and vomited just as do non-pregnant women. It requires 500 milligrams more of diethylstilbestrol in a single dose to produce the same nausea and vomiting in a pregnant woman that from 0.75 to 5.0 milligrams produces in the non-pregnant woman. In brief, the pregnant woman tolerates with 1000 times the dosage of diethylstilbestrol required to produce side effects in a non-pregnant woman. The liver in pregnancy can metabolize apparently up to 500 milligrams per day, and only 0.5 milligrams per day in a non-pregnant woman.

League, of New Orleans, (2) studying the toxicity of diethylstilbestrol in rats, calculated that it would require on the basis of body weight, about 7000 milligrams of diethylstilbestrol per day for 30 days to harm an average sized woman.

Other than the nausea and vomiting, which appears in from four to six hours after taking 0.75 to 5.0 milligram uncoated tablet of diethylstilbestrol, there was no "toxicity" demonstrable. Neither skin rash nor marked edema of the labia has been observed in any

of our cases. A slight amount of edema of the labia has been seen, however. The nausea and vomiting passes away in from four to six days if the drug is continued. It has been observed that there is no quantitative relationship of the nausea or vomiting in a non-pregnant patient, whether 5.0 or 250.0 milligrams is ad-

TABLE 2 COMPOSITION OF A SERIES OF 426 CASES OF GYNÉCIC DISORDERS AND AVERAGE TOTAL DOSAGE OF DIETHYLSTILBESTROL IN EACH CATEGORY

Condition	Number of Cases	Average total dosage (mg.)
Menometrorrhagia	221	115
Amenorrhea	20	40
Loss of libido	6	200
Hypoplastic uterus	1	40
Dysmenorrhea	27	15
Senile vaginitis	9	14
Sterility	1	100
Vulvovaginitis	5	40
Oligomenorrhea	6	40
Hypomenorrhea	19	40
Menopause	46	40
Painful breast	4	100
Acne of face	1	40
Hypoplasia of breast	1	80
Ovarian cysts	6	100
Ill feeling at menses	5	40
Menses research	25	800
Miscellaneous cases	23	500
	426	—

In this series of cases 2,057 laboratory determinations of various sorts were made. For the detection of any possible toxic influences blood sedimentation rates and complete blood counts were principally relied upon.

ministered at a single dose and every day thereafter for 30 days. Obviously these side effects do cause some nutritional imbalance, which is only transient however.

The only untoward effect observed was uterine bleeding which was seen in cases with an intact uterus and a patent cervix, and which were given 1.0 milligram (25,000 international units) of diethylstilbestrol daily for more than 25 consecutive days. This will occur in the normally menstruating woman. The production of uterine bleeding in the menopausal patient is quite alarming sometimes. No woman with an intact uterus should be given 1.0 milligram of diethylstilbestrol daily for a period of 30 or more days. This is especially true in the menopausal patient.

Further details are summarized in tables 1 and 2.

#### CONCLUSION

From an extensive series of observations in women given massive doses of diethylstil-

bestrol, one may conclude that there is demonstrable evidence to indicate that harmful changes result from such massive therapy.

Diethylstilbestrol is a non-toxic drug at the doses recommended in the literature followed.

This drug, in the pregnant woman, produces no nausea until a dose of 500.0 milligrams per day is given. It is suggested that the increase in liver metabolism permits increased dosages.

Diethylstilbestrol may be used without fear of serious consequence. It is a valuable drug.

The laboratory work as reported herein was carried out in the Jefferson Davis Hospital laboratory under the supervision of Dr. Donald G. Hendon, Dr. Peter Marcuse and Dr. W. W. Coulter, pathologists, and to D. Clair E. Folsome, I wish to express my appreciation.

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# EDITORIAL

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THE PRESENT NUMBER of the Journal marks the initiation of a new Section on "Methods and Technics." Its purpose is to provide space for the regular publication of special methods and technical procedures pertinent to the clinical investigation of endocrine functions. The Journal has in the past welcomed such communications, but the Editorial Board has recognized that numerous technical procedures of merit being utilized in laboratories throughout the country have not reached the pages of the Journal for various reasons. Thus, they may, for example, not appear to the originator to merit formal publication since they may represent modifications of existing methods. Nevertheless, such

modifications which serve to simplify or increase the accuracy of any procedure, deserve a more widespread circulation.

It is axiomatic that the development of any field of clinical investigation is, to a large extent, dependent upon the existence of reliable objective criteria for its study. It is hoped that the institution of this new Section will encourage laboratories to make brief communications relating to original procedures and to modifications of existing methods; and that it will thus serve to accelerate a wider use of reliable methods, and lead to a better standardization of procedures already in common use.





# METHODS AND TECHNIQUES

## A Rapid Method for Demucification and Staining of Seminal Smears

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**D**ETERMINATION of the incidence of various morphologic types of spermatozoa in the ejaculate is of value in establishing levels of fertility in the male (2-5). In order to insure satisfactory and routine clinical application, a method must be rapid, must eliminate artifacts and must permit delineation of all the cellular elements present in the ejaculate. To be of real practical value, moreover, a method should give consistent results which are readily reproducible by the same observer or by other workers. A serious handicap in attaining all these objectives is the presence of extra-cellular debris and mucus which interfere with interpretations of cell morphology. The present report describes a procedure which combines demucification with extremely rapid killing and fixation. This method employs a staining technic previously described by workers in our laboratory (1).

### PROCEDURE

Thin or thick smears are prepared in the usual manner after spontaneous liquefaction of the ejaculate has been established. Since the cells of some specimens have a tendency to clump after two hours, it has been found best not to delay making smears beyond this time.

<sup>1</sup> The expenses for these studies in part were defrayed by a grant from the National Committee on Maternal Health.

### *Killing and Fixation*

The smears are placed immediately in a mixture of absolute alcohol and ether for 10 seconds. This insures rapid fixation, which insures that all the cells will be retained on the slide and will stain homogeneously.

### *Dehydration*

1. Wash in 50% alcohol, 1 to 2 seconds.
2. Wash in distilled water, 1 to 2 seconds.

### *Demucification*

1. Place in acidified water (8 drops concentrated HCl to 40 cc. distilled water) until the slide is no longer opaque. This usually requires 1 to 2 minutes.
2. Wash in distilled water, 1 to 2 seconds.

### *Staining*

1. Stain with eosin (Eosin Y 1% aqueous solution), 30 seconds.
2. Wash in 50% alcohol, 1 to 2 seconds.
3. Stain in Harris' hematoxylin, 1 minute.
4. Wash in tap water, 1 to 2 seconds.
5. Stain in fast green (F. C. F. 0.5% aqueous solution), 1 second.
6. Wash in 95% alcohol, 1 to 2 seconds.
7. Wash rapidly in absolute alcohol, 1 to 2 seconds until slide appears clear of stain.
8. Clear in xylol, 3 minutes.
9. Cover with Clarite.

## RESULTS

The entire procedure requires about 9 minutes. Rapid killing and fixation permits retention on the slide of all the cellular elements of the ejaculate and prevents distortion which occurs with slow drying of the cells or fixation by heat. All the cells take the stain readily. The various components of the ejaculate are stained differentially as follows:

Mature spermatozoa		Developmental forms (Spermatocytes and Spermatids)	
Nucleus	pink	Nucleus	purple
Chromosome	blue	Cytoplasm	blue
Acrosome	green		green
Tail	green		

### Other Components

cytoplasmic fragments attached to certain immature cells	green
leucocytes (nuclei)	purplish to dark blue
large squamous epithelial cells of urethral origin	deep pink or green

## SUMMARY

A method of preparing seminal smears for morphologic study is described which combines rapid killing and fixation of cells with effective demucification. This procedure possesses the three-fold advantages of minimizing distortion, eliminating cell loss from the slide, and facilitating staining of all the cellular elements in the ejaculate.

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## GONADS

ABARBANEL, A. R.

The spasmolysant action of magnesium ions on the tetanically contracting human gravid uterus. *Am. J. Obst. and Gynec.* 49: 473 (1945).

The magnesium ion has immediate spasmolytic effects upon the tetanically contracting human gravid uterus. Magnesium will abolish tetany induced by posterior pituitary hormone, including pitressin, pitocin and pituitrin, quinine, ergonovine and methergine. The magnesium ion has no demonstrable effect upon the pattern of uterine motility in the first stage of labor but the author states it does have a definite analgesic effect. The clinical applications are discussed.—C.D.D.

ABEL, S.

Androgenic therapy in malignant disease of the female genitalia: preliminary report. *Am. J. Obst. and Gynec.* 49: 327 (1945).

Five patients with previously treated but progressively advancing malignancies of the uterine corpus and cervix were given testosterone propionate intramuscularly in arbitrary dosage of 140 to 150 mg. weekly. These patients have been treated for 10 months. Feeling of well-being, improved morale, control of menopausal symptoms and increased libido have been observed. To date, there is nothing to indicate any regression or retardation of the malignant process. With the dosage used, masculinization, including hypertrophy of the clitoris, development of a beard and voice change, has appeared in all 5 patients. Acneform eruptions have occurred in three. Vaginal smears have tended towards the atrophic state and have changed little during treatment. In one of these patients, metastatic lesions progressed during the course of treatment.—C.D.D.

KLOPP, C., N. F. YOUNG, AND H. C. TAYLOR, JR.

The effects of testosterone and of testosterone propionate on renal functions in man. *J. Clin. Invest.* 24: 189 (1945).

In four normal adult males, one eunuchoid male and four individuals with "disorders commonly associated with renal insufficiency," several functions of the kidney were studied before and after the administration of testosterone and testosterone propionate administered intramuscularly in daily doses of 90 to 300 mg. for periods varying from 8 to 29 days. The rate of glomerular filtration was measured by the clearance of mannitol. Renal blood flow was determined from the plasma clearance of sodium p-hippurate while plasma concentrations were maintained between 1.0 and 3.1 mg. per 100 cc. Tubular excretory mass was indicated by the clearance of sodium-p-hippurate when the plasma concentration of that compound was kept above 66.5 mg. per 100 cc. The maximum rate of tubular reabsorption of glucose was measured at plasma glucose concentrations above 350 mg. per 100 cc. The administered hormones were without measurable effect upon the functional capacity of the kidney under the conditions above noted.—T.H.McG.

MURPHY, D. P.

The role of the intermittent contractions of the uterus in the process of labor. *Am. J. Obst. & Gynec.* 49: 186 (1945).

Among the tracings of the uterine activity secured from some 1,800 patients when in labor, two individuals had records with no intermittent contractions. These observations were all made with the Lorand tocograph. In view of these findings, the author believes that as few efforts to be expended in initiating labor, or in improving labors of poor quality, should be directed primarily at some more fundamental purpose than in merely trying to influence the

of the uterus to contract intermittently.  
D.

SMANN, E. O.

velopment and degeneration of ovum and  
icle as observed by intravital staining.  
J. *Obst. & Gynec.* 49: 343 (1945).

ravital staining of cat ovaries was carried  
y the intravenous injection of indigo car-  
and trypan blue. Intact ova and granulosa  
do not take the stain. It is a sign of cellular  
or degeneration if the dye appears within  
ucleus or the cytoplasm. Intravital stain-  
indicates the beginning degeneration of the  
at a time when no change of structure is  
e. This demonstrates that degeneration of  
ollicle begins in the nucleus of the ovum,  
essing further to the ooplasm and finally  
granulosa cells. The zona pellucida of the  
ova takes intravital dyes and intimate  
actions between the zona and the inter-  
s between the granulosa cells are seen.  
onnection between the ovum proper and  
ona was visualized. This makes it probable  
the zona is deposited from the outside to  
vum. The author believes the liquor folli-  
depends closely upon the activities of the  
lation of blood and lymph for its origin,  
it is possibly modified by the influence of  
granulosa cells but definitely not by their  
faction. The author points out several  
ems to which an intravital staining tech-  
may be applied.—C.D.D.

## PANCREAS

BAKAY, L., JR.

generation of islands of Langerhans. *Vir-  
ows Arch. f. path. Anat.*, 310: 291 (1943).

icroscopic studies of thirty specimens from  
ts showed that postnatal island regenera-  
occurs under pathological conditions in  
with impairment of the entire pancreas,  
in cases of true diabetes, chronic pancrea-  
and pancreatic cirrhosis, or in cases in  
h the functional disturbance results from  
latory insufficiency (arteriosclerosis of the  
reas). The absence of any clinical symp-  
s of diabetes may be explained by the com-  
ating effect of an intensive regenerative  
ess in the islands of Langerhans. In addition  
he hypertrophy of epithelium in the excre-  
ducts, the increase in the insular system is  
to the transformation of the acini and to the

segmentation of the old islands. Traces of this  
regeneration could be found in almost any case  
of diabetes. From three to four new islands are  
sometimes present adjacent to the proliferat-  
ing excretory ducts. The regenerative tendency  
is suggested by the fact that in addition to the  
large hydropic islands, others may be found  
which consist of small, dense, dark-colored cells.  
They are surrounded by a ring of connective  
tissue which is thicker than that found in  
normal cases. Vessels are not found within  
these islands. Their rudimentary character ex-  
plains the absence of clinical improvement in  
spite of the regenerative process which was  
demonstrated on microscopic examination. Re-  
generation in the head of the pancreas in a pa-  
tient aged sixty-five suggested that the regen-  
erative capacity is not reduced with advanced  
age.—*Courtesy Diabetes Abstracts.*

BALLANTYNE, A. J.

Retinal changes associated with diabetes and  
with hypertension. A comparison and con-  
trast. *Arch. Ophthalmol.* 33: 97 (1945).

The retinopathies of diabetes and of the hy-  
pertensive diseases are separate entities both  
clinically and histologically. In both conditions  
the earliest recognizable lesions are pathological  
changes in the retinal vessels. In diabetes these  
affect primarily the venous, in hypertension the  
arterial side of the retinal circulation. In dia-  
betes these changes point to a venous stasis and,  
in addition to the familiar hemorrhages and  
exudates, include congestion of the veins, micro-  
aneurysms on the capillaries and gross changes  
in the principal veins. Microaneurysms may  
occur alone and seem to be the earliest recog-  
nizable change in the diabetic fundus. Occur-  
ring at the posterior pole of the fundus, alone  
or with a few punctate exudates, they are of  
great diagnostic significance. The microan-  
eurysms are found on the capillaries which pass  
through the inner nuclear layer to link the  
superficial and deep retinal plexuses. The most  
striking changes in the larger retinal veins of  
the diabetic appear as expansions, beading, and  
the formation of loops, coils and networks, and  
the predominant histological changes at this  
stage are phlebosclerosis and intra- and pre-  
retinal networks of large thin-walled vessels.  
The hemorrhages in diabetic retinopathy occur  
primarily in the central area of the fundus, are  
characteristically of rounded form, and are  
found chiefly in the deep layers, for the most

part the internuclear. In hypertension arterial changes predominate, the hemorrhages are primarily circumpapillary and striate in appearance, owing to their situation in the nerve fiber layer. Exudates are found in the deep layers, but also include patches of ganglioform degeneration in the nerve fiber layer. It is suggested that in both forms of retinopathy toxic factors are responsible for the initial vessel changes.—*Author's Summary.*

BARACH, J. H.

Normal standards in the treatment of young persons with diabetes. *Am. J. Dis. Child.* 69: 92 (1945).

After a review of present day standards of age-height-weight values, charts based on averages obtained from a large number of measurements are constructed. These charts portray the normal trends of growth from the ages of 1 to 21 years. On the basis of the generally accepted values for caloric requirement per day and daily protein requirement per kg. of body weight by growing children and of the amounts considered normal and adequate for children of various ages, a table of diets was constructed to serve as a standard for this study. The growth curves of 135 children with diabetes who had been under observation for 2 to 12 years were superimposed on the normal growth charts, and this revealed that some of the children were of normal size, others were below normal and the remainder were oversize. The caloric values of the diets on which these children had been subsisting were compared with those of normal or adequate diets, and it was found that some children attained normal

growth on diets of lesser caloric value than ordinarily prescribed and others did not attain normal growth regardless of the fact that they had been given diets of greater value than considered necessary for normal growth. The generously fed children required from 1 to nearly 2 times as much insulin as those who had been subsisting on conservative diets.—*Author's Summary.*

BLACK, D. R.

Experimental diabetes. *J. Missouri Med.* 41: 231 (1944).

The discussion follows lines that have been followed in everyday treatment, considering, first, the relation of various endocrine glands to diabetes; second, arteriosclerosis and capillary friability; and, third, diagnosis of the disease, with a discussion of the significance of glycosuria. In addition to consideration of the various extrapancreatic influences on the pathogenesis and course of diabetes, the fact still remains that the therapeutic approach to control of the disease at present is one of diet and proper insulin dosage. Heretofore, the renal threshold has been described as the blood-sugar level at which sugar appears in the urine. This point would be variable, of course, with the rise or fall of the blood sugar. In the light of present explanation, the renal threshold may be defined as that concentration of blood sugar at which the quantity entering the tubules per minute exceeds that which the tubules can reabsorb in the same interval. This is therefore apparent from Mirsky's report that the concentration of sugar in the urine is in itself an accurate index of the severity of diabetes.—*Courtesy Diabetes Abstracts.*



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# Effect of Testosterone Propionate on Losses Incident to Inadequate Dietary Intake<sup>1,2</sup>

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E. APPLETON, AND  
A. LINTON

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IT IS KNOWN that the ratio of potassium to nitrogen lost from the body during short periods of starvation with or without marked dehydration may exceed the ratio of potassium to nitrogen in normal muscle tissue (6, 10, 12, 13, 16, 32). It has also been observed that the administration of testosterone to subjects receiving an adequate diet may at least lead to a ratio of potassium to nitrogen retained in the body greater than that which obtains in normal muscle tissue (28, 29). In

such subjects the serum potassium may fall to extremely low levels (7, 28, 29). The administration of testosterone to an obese man during a period of submaintenance diet and weight loss resulted in a diminution in the urinary nitrogen output and an increase in the urinary excretion of organic acids (23). This observation suggests that testosterone diminishes the rate of utilization of protein or muscle tissue and necessitates an increase in the oxidation of fat to meet the energy requirements.

The availability of certain experimental data (10, 11) which could serve as controls led us to inquire further into the effect of testosterone on the metabolism of the inadequately nourished subject and its possible therapeutic use in preventing protein loss

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<sup>1</sup>Acknowledgement is made to the Schering Corporation, Bloomfield, New Jersey, for the provision of the testosterone propionate used in this investigation.

incident to the unavoidable starvation suffered by many patients. To this end supplementary experiments were carried out to determine in some detail the effects of intramuscularly administered testosterone propionate upon the losses of body substances by normal human subjects during six day periods of absolute or partial fasting.

#### METHODS OF STUDY

Four healthy young men from C.P.S. Camp No. 115 volunteered to be the subjects for these investigations. Their normal body weights were approximately as follows: *W.H.*, 75; *R.E.*, 67; *E.B.*, 70; and *P.J.*, 66 kilograms, respectively. The daily intake over the six day periods without testosterone and the six day periods with testosterone was for *W.H.* only 1000 cc. of water daily; for *R.E.*, 1000 cc. of water plus 50 gm. of glucose; for *E.B.*, 1200 cc. of water, 4.5 gm. of sodium chloride and 100 gm. of glucose; and for *P.J.*, 1000 cc. of water and 300 gm. of glucose. The important variable other than testosterone which concerns us in this study was the quantity of glucose. The variations in water and sodium chloride were incident to other studies.

The first time each subject had received his particular dietary regime for the six day period, he received no testosterone (10, 11). The second time, for eight days preceding the experimental period and for the six day period of the restricted regime he was given 25 milligrams of testosterone propionate intramuscularly daily. The two experimental periods were separated by a recovery period of at least one month.

During the experimental periods, the urine was collected in 24 hour lots. No stools were passed. In addition fasting blood was withdrawn for certain measurements on the morning of the 3rd and 6th days. Most of the methods of analysis are listed in a previous publication (28). In addition the following methods were also used: amino-acid nitrogen (31), organic acids (22),<sup>3</sup> acetone bodies (22),<sup>4</sup> milliosmols (21).

#### RESULTS

Considerable experience with previous studies over six day periods of starvation with very inadequate caloric intake (5, 10, 12) has shown that the renal excretion of various substances over the last four days of the period reflects with great consistency the effect of the experimental regime on the individual's metabolism. On the other hand, the urinary excretion of the first two days reflects the pre-period regime and condition of the subject as well as the experimental regime. Accordingly, in the presentation of these data emphasis has been placed on those pertaining to the last four days.

The data of figures 1 to 4 (left hand portions) show that during the last four days of periods of testosterone propionate administration all subjects excreted less total nitrogen (average decrease, 33 mg. per day) than they did during control periods. This decrease in total nitrogen excretion was due to a diminution in the urinary output (average decrease, 34 mg. per day). The effect of the varying amounts of glucose per se upon the elimination of total nitrogen is shown in figure 5. The largest excretion values per kg. of body weight were obtained for subject *W.H.*, who received nothing but water. The administration of 50 grams of glucose resulted in a moderate decrease, while the administration of 100 grams of glucose prompted a greater decrease in the total urinary nitrogen as did 300 grams of glucose. The output of urea of total nitrogen tended to diminish from the 3rd to the 6th day of the experimental period both with and without testosterone.

Figure 6 reveals that testosterone propionate also tended to cause a slight increase in the preformed creatinine excretion, a decrease in the output of creatinine. The increase in preformed creatinine was an average 1.2 milligrams per kilogram per day. This value is approximately six per cent of the value for the average excretion of preformed creatinine during the control period. On the other hand, the decrease in creatinine averaged 1.6 milligrams per kilogram per day, a value equal to 37 per cent of the average

<sup>3</sup> Page 647.

<sup>4</sup> Pages 626-629.

creatinine output during the control periods. The testosterone therapy did not enhance the urinary excretion of ammonia amino acids; the average elimination of

H 1,000 CC H<sub>2</sub>O, 0 GM. GLUCOSE Q D.

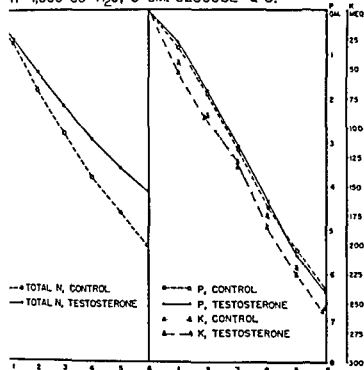


FIG. 1. Effect of testosterone propionate therapy (25 mg per day i m) on the daily urinary total nitrogen (left section), potassium and phosphorus losses (right hand section) of subject *W.H.* during six day periods of absolute nitrogen balance. The meaning of the symbols is given at the bottom of the figure. The points defining the lines were determined by the excretion value of that day to the value for the preceding day.

H 1,000 CC H<sub>2</sub>O, 50 GM. GLUCOSE Q D

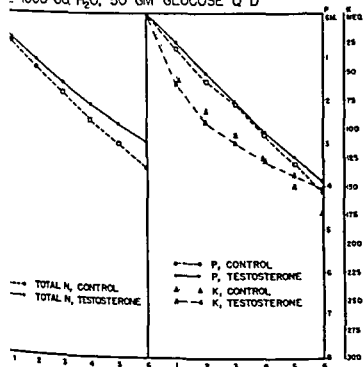


FIG. 2. Effect of testosterone propionate therapy (25 mg per day i m) on the urinary total nitrogen, potassium and phosphorus losses of subject *R.E.*, who received 50 gm of glucose daily. The design of this figure corresponds to that of figure 1.

E.B 1200 CC H<sub>2</sub>O, 100 GM. GLUCOSE, 45 GM. NaCl Q D

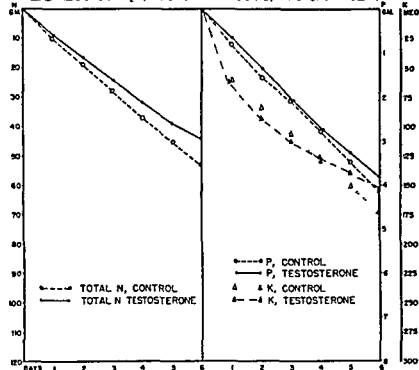


FIG. 3. Effect of testosterone propionate therapy (25 mg per day i m) on the urinary total nitrogen, potassium and phosphorus losses of subject *E.B.* who received 100 gm of glucose daily. The design of this figure corresponds to that of figures 1 and 2.

P.J 1000 CC H<sub>2</sub>O, 300 GM. GLUCOSE Q D.

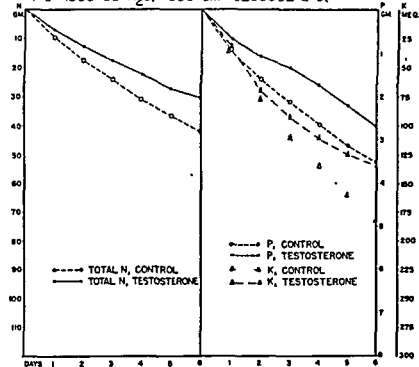


FIG. 4. Effect of testosterone propionate therapy (25 mg per day i m) on the urinary total nitrogen, potassium and phosphorus losses of subject *P.J.* who received 300 gm of glucose daily. The design of this figure corresponds to that of figures 1 to 3.

amino acids by the subjects during both the control and testosterone periods being approximately 1.0 milligram per kilogram per day.

With the exception of *W.H.* (0 gm. glucose), the elimination of potassium was appreciably less during periods on testosterone than during control periods (right



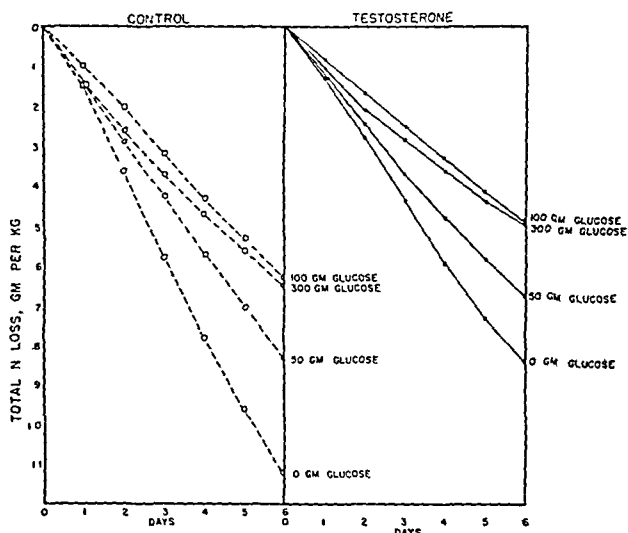


FIG. 5. Effect of various inadequate diets and of testosterone upon the urinary excretion of total nitrogen by the subjects of Figures 1 (*W.H.*, 0 grams glucose), 2 (*R.E.*, 50 grams of glucose), 3 (*E.B.*, 100 grams glucose) and 4 (*P.J.*, 300 grams glucose). The left hand portion of the figure represents control periods; the right hand portion represents periods on testosterone.

hand sections, figures 1 to 4). The average difference for the four subjects during last four

days of the periods was 0.09 milliequi per kilogram per day. However, for each subject the potassium excretion during the testosterone period exceeded or equalled potassium excretion on at least one corresponding day of the control period. This contrast to the uniformly diminished nitrogen excretion for all subjects on all days of testosterone periods.

The phosphorus excretion (see right sections, figures 1 to 4) was on the average less during the last 4 days of period on testosterone (average 0.0097 gm. per kg. per day) than during the corresponding control periods (average 0.0106 gm. per kg. per day). There was no difference for subject, *W.H.*, who received no glucose, whereas the greatest difference (average 0.017 gm. P per kg. per day) was for subject, *P.J.*, who received 300 gm. glucose daily. A tendency for the phosphorus excretion to diminish as the quantity of glucose in the diet was increased was also

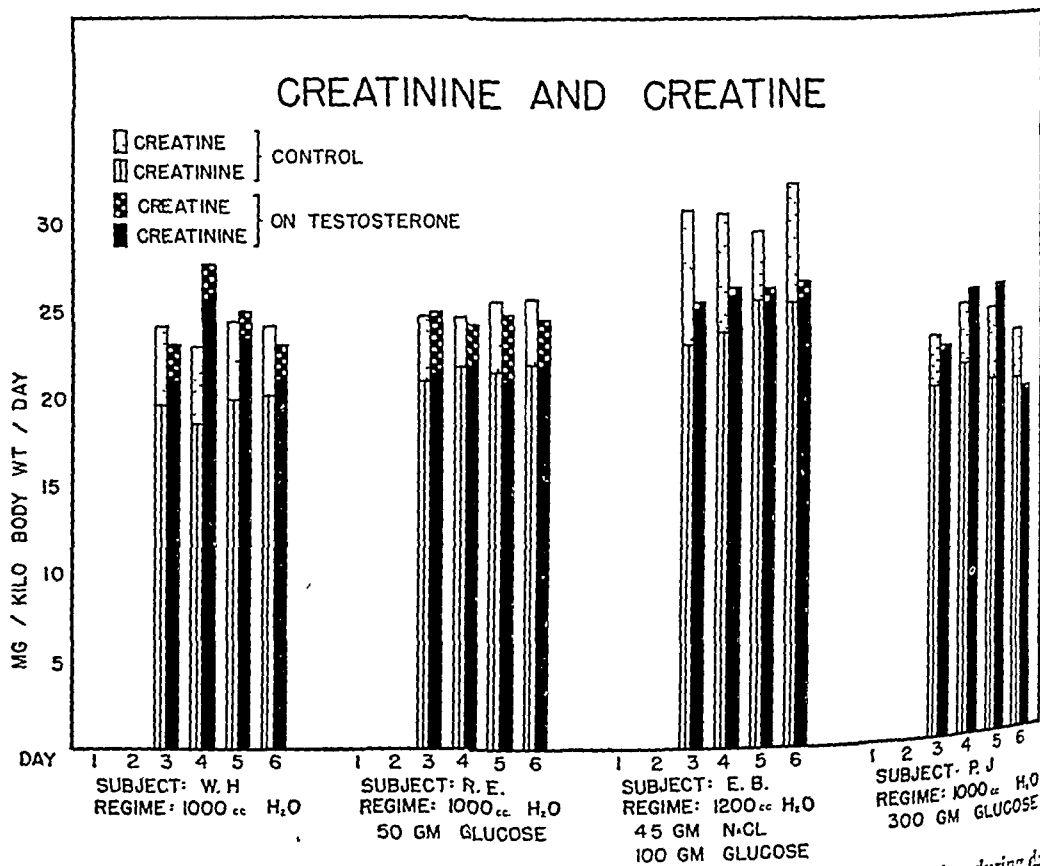
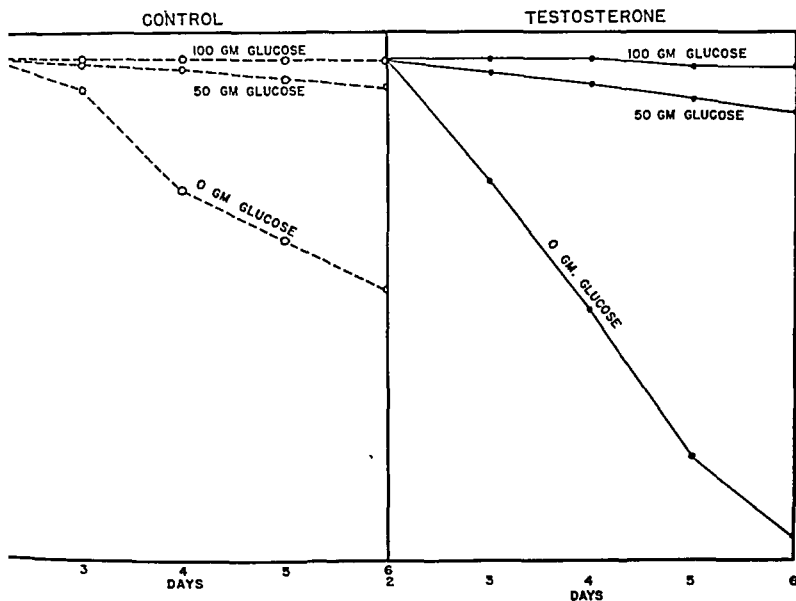


FIG. 6. Effect of testosterone propionate upon urinary preformed creatinine and creatine excretion during six six-day periods of inadequate dietary intake. The subjects and dietary regimes are the same as those of Figure 5. A legend in the top left quadrant gives the meaning of the columns. A scale in milligrams of creatinine or creatine (both expressed as creatinine) excreted per kilogram of body weight per day is given along the left hand ordinate.

ures 1 to 4 also permit a consideration of ratios of potassium to nitrogen and of phosphorus to nitrogen excreted during the control and testosterone periods. It will be noted that the scales for nitrogen, potassium and phosphorus are so designed that a horizontal line drawn across the figures at

eliminated in about the same proportions as exist in muscle tissue. On the other hand, when the curves for phosphorus or potassium have a steeper slope than the curve for nitrogen, then the ratio of potassium to nitrogen or of phosphorus to nitrogen lost exceeds that characteristic of true muscle



Effect of testosterone and of diet upon the urinary output of acetone bodies. The subjects are the same as those of preceding figures (*W.H.*, 0 grams glucose, fig 1, *R.E.*, 50 gm glucose, fig 2, *E.B.*, 100 gm glucose, fig 3).

level intersects the three scales at values which bear approximately the same relation to each other that pertain for nitrogen, potassium and phosphorus in true muscle tissue. Accordingly, when the curves depicting urinary nitrogen, potassium and phosphorus excretions, respectively, have the same slope, these substances are being

discussed previously, in true muscle there are approximately 2.86 milliequivalents of potassium per gram of nitrogen (28). The ratio of phosphorus to nitrogen is approximately 0.067 grams P to 1 gram N (24). In figures 1 to 4 the scales are drawn for convenience in such a manner that multiples of 2.5 milliequivalents of potassium, 0.067 grams of phosphorus and 1 gram of nitrogen fall on horizontal lines.

tissue. Such high ratios are evident in figures 1 to 4 and especially in figure 1 (*W.H.*, 0 gm. glucose). In this figure it can also be seen that while testosterone diminished the nitrogen output, it had essentially no effect on the phosphorus or potassium output. Accordingly testosterone therapy resulted in higher P/N and K/N ratios in this subject. However, for the subjects of Figures 2 to 4 who received varying amounts of glucose, testosterone treatment had only a slight and irregular tendency to increase the P/N and K/N ratios. On the other hand, it is of interest that while these three subjects ex-

creted potassium as rapidly during the first two days of the testosterone periods as they did during the first two days of the control periods, they tended to excrete less during the last four days while receiving testosterone.

The urinary excretion of acetone bodies is shown in figure 7. Here is observed a consistent and striking tendency for inadequately fed subjects to excrete more of these substances when receiving testosterone propionate than during control periods. This

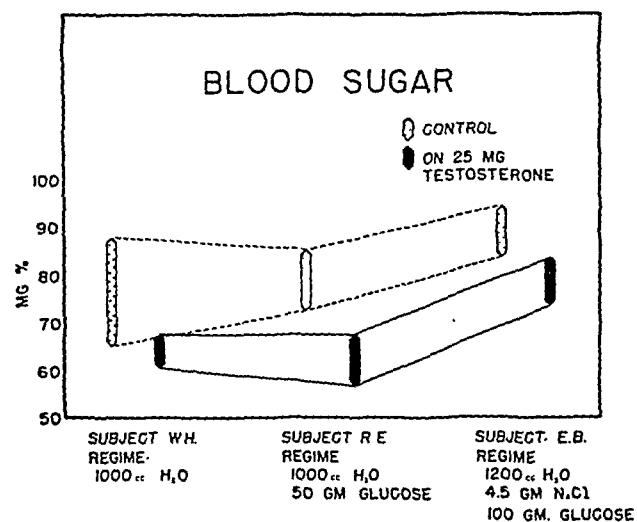


FIG. 8. Effect of testosterone propionate upon fasting blood sugar concentrations during periods of inadequate dietary intake. The subjects and their regimes are the same as those of figures 1-6. The length of the double headed arrows (light speckled for the control periods; black for the periods of testosterone therapy) indicates the range of the fasting blood sugars during days three to six of the six day periods. A scale in milligrams of glucose per 100 cc. of whole blood is presented along the left hand ordinate.

tendency was most marked in the subject who received no glucose and was less striking, the larger the glucose intake. The curves representing *P.J.* (300 gm. glucose) are not shown because he excreted essentially no acetone bodies during either regime.

Figure 8 presents the range of fasting blood sugar concentrations of the subjects who received 0, 50, and 100 gm. of glucose per day, respectively. It is seen that these blood sugar values were consistently higher during control periods than during testosterone periods.

The administration of testosterone propionate did not induce any significant changes in the concentrations of serum

sodium, chloride, phosphorus or protein. The serum potassium varied but little.

Table 1 summarizes much of the foregoing information and presents certain other data not previously mentioned; namely, body weight loss and urinary sodium, chloride, organic acids, and milliosmol excretion. The values given are averages for the last five days of the experimental periods. Except for subject, *W.H.*, there was a decreased weight loss during the testosterone periods. This exception is believed to be due to an increased loss of sodium- and chloride-containing extracellular fluid because of excess perspiration due to hot weather as evidenced by a measurable increase in extra-renal water loss. Except for this complicating factor in this experiment, testosterone propionate appeared to favor a slight reduction in the urinary loss of sodium and chloride. Incidentally, the data of the control periods of *W.H.*, *R.E.*, and *P.J.* exemplify the recently observed effect of small amounts of ingested glucose on reducing the urinary loss of sodium and chloride incident to starvation (10, 11). A slight reduction in the urinary milliosmols during periods on testosterone propionate were noted in the three subjects not affected by hot weather.

#### COMMENTS

The reduction during the testosterone periods in the urinary excretion of total milliosmols, nitrogen, potassium and phosphorus by these fasting or partially fasting subjects is in general agreement with the increased retention of these substances that is known to result from the administration of testosterone propionate to individuals receiving an adequate diet (1, 8, 14, 15, 18-28-30). The increased excretion of preformed creatinine and the decreased excretion of creatine have already been noted and commented on by others (8, 14, 15, 28).

The increase in acetone body excretion and hence in organic acid output in the testosterone periods confirms the observations on the obese subject (23) receiving an adequate caloric intake referred to in the introduction. The tendency towards a

in fasting blood sugar values in association with the increased urinary output of stone bodies and decreased urinary urea suggests diminished gluconeogenesis during testosterone periods. The tendency of testosterone to cause an increase in the ratios potassium to nitrogen and of phosphorus to nitrogen in the urine of the present sub-

ject is a compensatory increase in the catabolism of fat (2).

In these respects Benedict's observations on the fasting subject, *L.*, may be pertinent (3) Figure 9 describes the calculated sources of energy expended by *L.* during the first six days of his 30 day fast. During the first three days, approximately 13 per cent of the

TABLE I AVERAGE LOSSES OF BODY WEIGHT AND OF VARIOUS URINARY CONSTITUENTS DURING DAYS THREE TO SIX INCLUSIVE, OF CONTROL PERIODS AND OF PERIODS ON TESTOSTERONE PROPIONATE. RESULTS EXPRESSED AS UNITS PER KILOGRAM PER DAY

Substance lost	Subject							
	<i>W H</i> Fasting		<i>R E</i> 50 gm. glucose		<i>E B</i> 100 gm. glucose		<i>P J</i> 300 gm. glucose	
	Control	Testosterone	Control	Testosterone	Control	Testosterone	Control	Testosterone
Actual body wt., kg	71.0	72.4	63.4	65.0	66.9	70.7	64.3	61.3
Body wt. loss, gm	10.7	11.2	8.6	8.2	7.6	5.3	4.4	4.0
<i>Urinary Losses*</i>								
Total N, mg	190	142	136	108	106	80	96	72
Urea N, mg	154	103	109	85	80	58	76	49
H <sub>2</sub> N, mg	15.6	17.1	9.1	9.3	4.8	3.3	5.3	5.6
Umino acid N, mg	0.97	1.08	0.88	0.90	0.99	1.04	1.17	1.11
Creatinine N, mg	7.3	8.5	8.1	8.0	9.1	9.5	7.7	8.7
Ureatine N, mg	1.38	0.67	1.15	0.99	2.05	0.8	1.12	0.06
Urea, mg	15.8	15.7	10.3	9.5	8.8	7.6	7.5	6.5
Urea, meq	0.584	0.568	0.353	0.229	0.468	0.348	0.408	0.280
Urea, meq	0.546	0.755*	0.245	0.224	0.990†	0.868†	0.043	0.058
Urea, meq	0.391	0.526*	0.271	0.230	1.000†	0.887†	0.097	0.148
Organic acids, meq	1.48	2.22	0.70	0.77	0.66	0.58	0.80	0.61
Stone bodies, mg	57.3	118.6	6.9	13.5	1.4	2.6	0.8	1.0
Uric acid, mg	10.9	10.6	6.4	5.5	7.4	5.5	4.6	3.4

\* Because the weather was hot during this period, the loss of water, sodium and chloride was probably greater than it would have been.

† The subject received 4.5 gm. of NaCl during these periods.

ject is in contrast to the decrease in the potassium to nitrogen ratio that may follow administration to adequately fed subjects (1, 29). This increased urinary excretion of potassium and phosphorus relative to nitrogen in the testosterone periods may well reflect the liberation of glycogen-bound potassium and phosphorus as the result of an accelerated or increased glycogenolysis (9). The foregoing observations, taken together, suggest that testosterone therapy alters the relative rates at which protein, fat and carbohydrate are catabolized by subjects receiving an inadequate caloric intake. They support the thesis that testosterone inhibits the utilization of protein or muscle tissue as a source of required calories and that there

calories were derived from carbohydrate and 13 per cent from protein. Fat provided the remainder of the caloric requirements. However, by the 4th day, the carbohydrate stores (glycogen) became depleted, so that only 1 or 2 per cent of calories were provided by the oxidation of carbohydrate, while about 19 per cent were obtained from protein oxidation and 80 per cent from fat. As the calories provided by carbohydrate diminished, the calories provided by the combustion of protein tended to increase. A slight decrease in the caloric expenditure is also noted.

The total urinary nitrogen excretion per kilogram per day of Benedict's subject, *L.*, and of subject *W H* of the present studies

while on and while off testosterone are plotted in figure 10. The values for the nitrogen excretion of *W.H.* during days three to six of his control experiment correspond closely to those of Benedict's subject, *L.* On the other hand, during days three to six of the

sistence of the effect of testosterone lowering the fasting blood sugars, even when 100 grams of glucose was eaten (*E.I.*) would appear to be due to the at least partial dependence of the concentration of glucose in the blood of such an inadequately nourished individual 12 hours after the last ingestion of limited amounts of glucose upon gluconeogenesis from protein.

In view of the marked reduction of acetonuria resulting from the ingestion of 50 gm. of glucose per day (fig. 7), the 50 gm. reduction in gluconeogenically available glucose to *W.H.* in the testosterone period might explain the increase in the excretion of acetone bodies in that period (4, 19, 20, 26). The diminishing effect of testosterone on acetonuria with increased ingestion of glucose, while its depression of nitrogen output continued throughout all the experiments, also supports the idea that the increased acetonuria reflected an increased catabolism due to caloric deficit.

Are these observed effects of testosterone propionate on an individual receiving

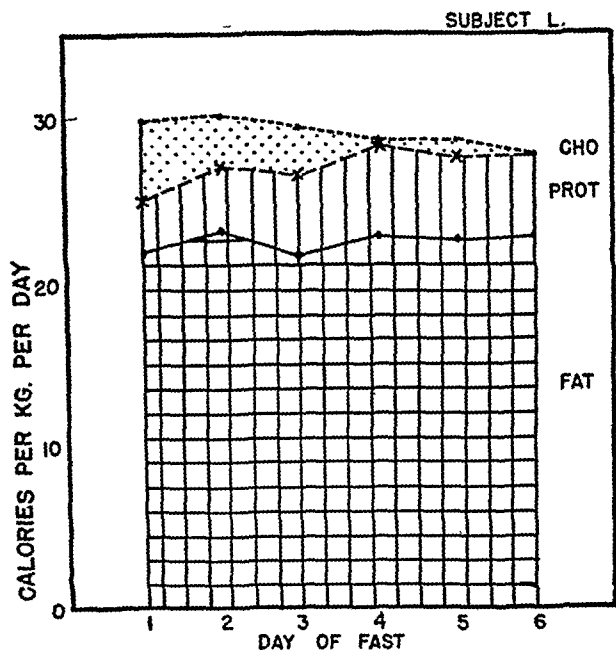


FIG. 9. A diagram of the calculated sources of energy for Benedict's subject, *L.*, during the first six days of his 30 day fast (25). The checkered area indicates the calories derived from the oxidation of fat; the vertically lined area, those derived from protein; and the speckled area, those derived from carbohydrate according to the scale given along the left hand ordinate.

experimental period on testosterone propionate, *W.H.* excreted about 0.05 grams per kilogram per day less nitrogen in the urine. In terms of total daily difference for *W.H.* this amounts to a reduction of 3.6 grams (0.05 gm. per kg.  $\times$  73 kg.) of urinary nitrogen or approximately 25 per cent. This indicates that approximately 22 grams less of body protein were catabolized per day. Such a decrease in protein catabolism would diminish the calories from that source by about 90 calories per day or five per cent of the daily energy requirement. It would also reduce by 13 grams the quantity of glucose made available by deamination of amino acids (18).

Possibly this reduction in glucose explains the tendency to lower fasting blood sugar values noted above (Figure 8). The per-

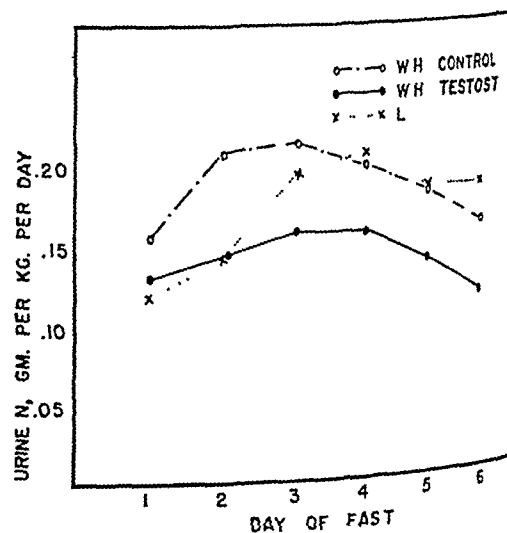


FIG. 10. The total urinary nitrogen excretion of Benedict's subject, *L.* (crosses connected by interrupted line) and of the present subject, *W.H.*, while off (circles connected by dots and dashes) and on testosterone (circles connected by solid line) according to scale *c* along the left hand ordinate.

inadequate dietary intake beneficial? Viewed quantitatively the daily saving of 22 gm. of body protein for the fasting subject, *W.H.*

ounted to about 0.2 per cent of his ginal muscle mass per day.<sup>6</sup> Such a con- vation can hardly be considered important short periods. Moreover, it was ac- panied by an uneconomical expenditure potential energy from body fat as evi- ced by the ketonuria. On the other hand, importance of such tissue protein con- vation over long periods of inadequate tary intake cannot be determined until s known whether death from starvation ults from insufficiency of fuel or from ular depletion. Perhaps light may be own on this question by determining the ct of testosterone on the survival time of rving animals. Preliminary experiments h rabbits do not indicate that testos- one exerts a striking influence upon the vival period.

#### SUMMARY AND CONCLUSIONS

The effects of testosterone propionate rapy upon the urinary excretion of vari- nitrogenous substances, minerals, organic ds and acetone bodies of four healthy ung men receiving an inadequate dietary ke have been studied. In addition changes the concentrations of blood sugar and of um electrolytes were measured.

It was found that testosterone propionate ded to reduce the urinary output of total, a and creatine nitrogen and of potassium l phosphorus and to increase the excretion reatinine, organic acids and acetone bod-

The effect of this agent upon body weight ses and upon the total urinary solutes (mOsmols) was appreciable but small. The ministration of testosterone propionate reted in lower fasting blood sugar values. It l little or no effect upon the concentrations the serum electrolytes or upon the urinary ination of amino acids or ammonia.

It is concluded that though this hormonal therapy does conserve small quantities of tissue protein under conditions of fasting, it does not result in a significant saving of body substance as a whole. There is no evidence that it diminishes the energy requirements of the starving person. Furthermore, by conserving protein, it interferes with glu- coneogenesis from protein. As a consequence of the reduction in available sugar, there ap- pears to be an increased and a less efficient oxidation of fat. With the information at hand, it is difficult to state whether or not such a conservation of protein at the expense of fat and of gluconeogenesis is beneficial for a person receiving an inadequate dietary in- take.

The authors wish to acknowledge their ap- preciation of the eager and intelligent coop- eration of the volunteer subjects which so contributed to the accuracy of these studies.

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<sup>6</sup>The original muscle mass was estimated from the ary excretion of preformed creatinine per day (1 gram tline=17.8 kg. muscle) as discussed elsewhere (27). mular value is obtained by assuming that the muscula- comprises about 45 per cent by weight of the total y tissues of a normal young man (18). The muscle mass assumed to be 70 per cent water and 30 per cent pro- (28).

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# The Enhancement of Tuberculous Infection in the Guinea Pig by Steroid Hormones

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AMONG the many factors which long have been considered in various studies on the reaction of different individuals to infection with the tubercle bacillus, the idea of constitutional differences is even older than our knowledge of the tubercle bacillus itself. Hirsch (11) stated that phthisis (tuberculosis) appears in successive generations of certain families regularly to deny hereditary elements. The recent studies have established the validity of these early observations both by the experimental approach [Lurie (13)] and the epidemiologic method [Puffer (14)]. In addition to these broader host or constitutional differences, variations in tuberculosis mortality import in the two sexes are well known.

As pointed out by Dauer (7), during the last 75 years there has been little change in the ratio of female to male mortality between 15 and 29 years of age, although total mortality from tuberculosis has been steadily declining. It appears that the factors responsible for the difference in the ratio of female to male deaths from tuberculosis has remained constant, and is unrelated to the factors to which the general decline in mortality has been attributed. Puffer (14) has pointed out that mothers (of index cases of tuberculosis in her study) born after 1860 showed the same mortality from tuberculosis as did those born prior to 1860. This difference is further emphasized by the observation [Dauer (7)] that tuberculosis mortality, although low, is about equal for

both sexes in children less than 5 years of age, while mortality is declining much more rapidly in females over 30 years of age than in males of the same age groups. In her studies on familial susceptibility Puffer (14) also pointed out that the incidence of manifest tuberculosis in female siblings of index cases was nearly twice that among male siblings of the same families. Similarly, the incidence among female siblings of consorts was higher than that observed in the male siblings of consorts. Tuberculosis mortality, although varying with the degree of exposure, (both, one or neither parents tuberculous) was consistently higher among female siblings than among male siblings.

In addition to observations such as these on the differences in the incidence and mortality from tuberculosis between the sexes, an unfavorable effect of pregnancy in tuberculous females also has been recorded [Brack and Gray (5)], suggesting that among other factors alterations in the economy of the sex hormones in some way might result—as they appear to do in certain other diseases—in alterations in host resistance to tuberculosis. The experimental data indicate that the estrogenic substances exhibit a favorable action on a number of experimental infections. Aycock (2 a, b) showed that treatment of monkeys with estrogenic substance enhanced resistance to poliomyelitis following intranasal instillation of the virus. Sprunt, McDearman, and Raper (16) reported that treatment with estrogenic substance increased the resistance of rabbits to vaccinia virus. Von Haam and Rosenfeld (18) demon-



strated the protective action of these substances against experimental pneumococcus infection in mice, while Foley and Aycock (8) reported similar protective action for stilbestrol against experimental streptococcal infection in mice.

Attempts to demonstrate some action—favorable or otherwise—on host resistance by the use of various endocrine hormones in experimental tuberculosis have been numerous and contradictory. Vercessi and Merenda (17), Repetti (15), Bourgeois and Bouget (3), and Gray and Brack (9) reported that various estrogenic substances exhibit little or no effect on experimental tuberculosis. Similarly, Green and Morgan (10) and Carnes and Biskind (6) reported that progesterone and testosterone respectively did not affect the course of the experimental disease. Conversely, Addressi (1) reported that rabbits treated with pregnant mare's urine died sooner of bovine tuberculosis than did normal control animals infected with the same strain. Bourgeois *et al.* (4) found that castration of guinea pigs prolonged the survival time following injection of tubercle bacilli. Injection of estrogenic substance (folliculin) and gonadotropic hormone accelerated the course of the disease in the female guinea pig while treatment with male hormones prolonged the survival time of male guinea pigs. Long and Vogt (12) observed that ovariectomized mice developed less severe tuberculosis at the height of the disease than either intact control mice or ovariectomized mice treated with theelin. The low mortality in the ovariectomized group, and the shorter survival time in the theelin-treated group suggested that in some way ovariectomy is protective and estrus harmful with respect to experimental tuberculosis.

The discrepancies in these reported results may be due in part to the use of different hormone preparations of varying potency and to the use of different strains of tubercle bacilli—some stock cultures are of relatively low virulence. Few experiments have been reported in which chemically pure crystalline hormones of standardized potency and

freshly obtained strains of human tubercle bacilli were used. Aycock has noted monkeys treated with stilbestrol often develop an unusual spontaneous tuberculosis involving the mammary and axillary lymph system. For these reasons, the following experiments were undertaken.

#### METHODS

In the experiments reported here, pooled and digested sputa from active cases of tuberculosis were compared in normal guinea pigs and guinea pigs injected with crystalline estrogenic substances in oil.<sup>1</sup> In the first experiment, an equal number of normal intact male and female guinea pigs (animals) 200–250 gm. in weight were given 0.05 mg. of alpha-estradiol dipropionate (Progynon-DP)<sup>2</sup> subcutaneously in 0.5 ml. of sterile, sesame oil. This product although less potent than the benzoate salt, had a prolonged effect following injection. Changes in the genitalia were apparent the day following administration. Forty-eight hours after injection of the alpha-estradiol dipropionate, these animals and a similar number of male and female controls were given subcutaneously in the inguinal region 0.5 ml. of a digested pool of six sputa collected the same day from active cases of tuberculosis. After pooling, the sputa were digested by the sodium hydroxide method (Wadsworth,<sup>11</sup>) and concentrated to 1/10 the original volume in normal saline. Thereafter the estrogen-treated animals received 0.05 mg. dose of alpha-estradiol dipropionate at intervals varying from 24 to 72 hours as indicated by examination of the genitalia. The second experiment (10 animals) was identical with the first except that the estrogen-treated animals received a total of 0.5 mg. of alpha-estradiol dipropionate as 10 doses of 0.05 mg. each at 24 hour intervals prior to injection of the sputa-digest. The animals surviving

<sup>1</sup> A series of control animals injected with alpha-estradiol dipropionate in sesame oil in the same manner as the experimental animals was included in these experiments. Guinea pigs treated after two, four, six, and eight weeks of such treatment showed no gross pathologic change other than some accumulation of fat in the omentum.

<sup>2</sup> We wish to thank Dr. W. R. Bond, Schering Corporation, for his kindness in supplying these products.

full course of the experiments received total of 1.65 mg. and 3.55 mg. of alpha-estradiol dipropionate respectively in the first and second experiment.

A similar experiment was done substituting testosterone propionate (Oreton)<sup>2</sup> for the alpha-estradiol dipropionate. The animals treated with this substance received a total of 80 mg. as 16 doses of 5.0 mg. each in 0.2 cc. of sesame oil at 24 hour intervals preceding injection of the sputa-digest. Subsequent doses were administered as indicated by the genital reaction. Animals surviving the duration of the experiment received a total of 220 mg. of testosterone dipropionate. All animals were observed for 56 days. Animals dying early and those surviving 56 days were autopsied and examined for gross and bacteriologic (smear) evidence of tuberculosis. Certain of the normal control guinea pigs which died suddenly within a few days of the time of injection of the sputa-digest did not show evidence of tuberculosis at autopsy (hence omitted from the tables), but did present postmortem changes suggestive of acute upper respiratory infection. Such deaths were more common in the experiments done during the winter months, and, as it happened, did not appear to occur among the estrogen-treated animals, but whether or not this represents a protective effect of the estrogen against acute upper respiratory infection is not known. Four control guinea pigs were kept beyond 56 days until they died, two at 72 days and two at 84 days respectively. The guinea pigs killed after 56 days (tests and controls) are not included in the computations. The average incubation periods represent minimal values since the experiments were terminated at 56 days. Moreover, as will be discussed later, there is some evidence that death in a tuberculous guinea pig may be a chance phenomenon, the time of death being more or less unrelated to the extensiveness of infection.

#### RESULTS

Since the results of separate experiments with alpha-estradiol dipropionate were essentially the same, all experiments are com-

bined in table 1. It will be seen (table 1) that guinea pigs treated with alpha-estradiol dipropionate succumbed to injection of the sputa-digest earlier than did the normal control animals injected with the same material. Testosterone propionate appears to exhibit a similar but less marked effect, since these animals received a relatively larger dose of this substance. Tuberculosis mortality by weeks following injection of the sputa-digest is shown in figure 1. Mortality in the alpha-estradiol dipropionate or testosterone propionate-treated guinea pigs was consistently higher than that observed in the control animals.

At the end of 56 days, the period for which a guinea pig is usually kept in tuberculosis diagnostic work, the mortality in the alpha-estradiol dipropionate-treated group (91%) was significantly higher than that (47%) of the control (untreated) group (table 1). Mortality in the testosterone propionate-treated group (83%) was significantly higher than that of the control group, but did not differ from the mortality in the alpha-estradiol dipropionate-treated group. The average incubation period, as measured from the time of injection to the time of death in the normal control guinea pigs, was 50 days, 1.9 times that of the alpha-estradiol dipropionate-treated group, 26 days. The average incubation period in guinea pigs treated with testosterone propionate (34 days) was intermediate between the other two groups.

Although the control guinea pigs which survived 56 days following injection of the sputa-digest all showed evidence of tuberculosis at autopsy, the alpha-estradiol dipropionate-treated animals would have provided much earlier diagnoses (in most cases) had these been diagnostic animals. In addition to the shorter average incubation period and the higher mortality, it was observed that the alpha-estradiol dipropionate-treated animals presented evidence of a much more severe, generalized tuberculous infection than did the normal controls. The distribution and frequency of tuberculous lesions in the testosterone propionate-treated group resembled that of the alpha-

estradiol dipropionate-treated group but in general, infection was less severe. The frequency with which tuberculous lesions were observed in different organs in the three groups of animals is summarized in table 2.

In view of these results, the effect of estrogenic substance on the course of experi-

sputa-digest collected and treated as previously described. At the same time identical experiment with diethylstilbestrol was done with a similar number of female guinea pigs. The test-animals given 0.1 mg. doses of diethylstilbestrol regular 24 hour intervals (except week-

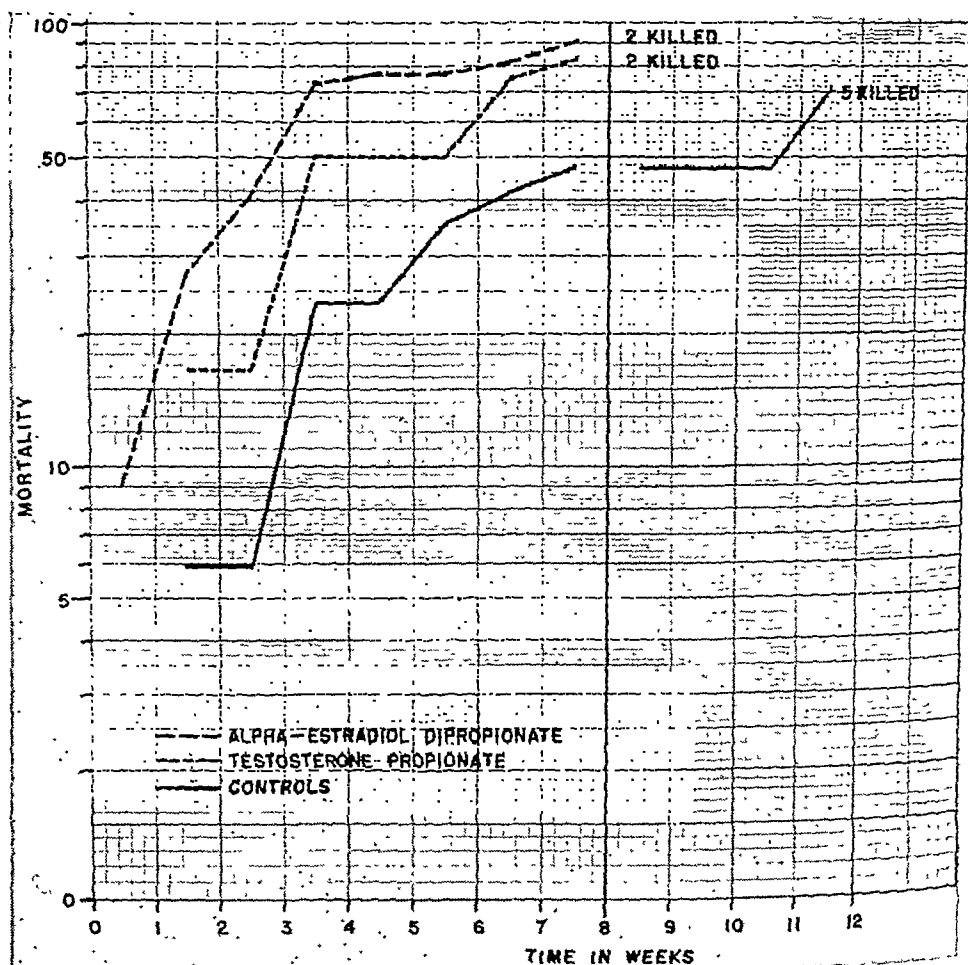


FIG. 1. Cumulative Mortality in Hormone-treated and Control Guinea Pigs Injected with Pooled Sputa-digest from Active Cases of Tuberculosis

mental tuberculosis in castrate animals was studied in a smaller series of guinea pigs. Bilateral ovariectomy was performed on 10 normal female guinea pigs of 200–250 gm. in weight. Seven weeks later these animals were divided into two groups, one of which was treated with 0.6 mg. crystalline diethylstilbestrol<sup>3</sup> administered as 0.1 mg. doses in 0.5 cc. sterile peanut oil subcutaneously at 24 hour intervals. These and the control animals were then given 0.5 cc. of a

Animals surviving the entire course of experiment received a total of 3.3 diethylstilbestrol. All survivors (56) were killed and autopsied. Although this series is small, the results (tables 3 and 4) with diethylstilbestrol in castrate and intact female guinea pigs were consistent with those of the previous experiments. The severity of the disease, as judged by the distribution of tuberculous lesions at autopsy was similar to that observed in the other experiments, viz., the diethylstilbestrol treated animals

<sup>3</sup> Product of E. R. Squibb & Sons.

TABLE 1. EXPERIMENTAL TUBERCULOSIS IN HORMONE-TREATED AND NORMAL GUINEA PIGS: AVERAGE INCUBATION AND MORTALITY

Hormone	No. animals	No. deaths in 56 days	Mortality		Average incubation	Survived 56 days
			21 days	56 days		
Alpha estradiol dipropionate	22	20	40.9	90.8	26.4 days	2*
Testosterone propionate	12	10	16.6	83.1	34.0 days	2†
None—normal controls	17	8	5.9	47.0	49.9 days	9‡

\* At autopsy 1 pig had tuberculosis, 1 was negative.

† At autopsy both pigs had tuberculosis.

‡ At autopsy all pigs had tuberculosis.

TABLE 2. EXPERIMENTAL TUBERCULOSIS IN HORMONE-TREATED AND NORMAL GUINEA PIGS: ANATOMICAL DISTRIBUTION OF LESIONS AT AUTOPSY

Site of lesion	Treated animals				Untreated controls	
	Alpha-estradiol dipropionate		Testosterone propionate			
	Dead in 56 days (20 pigs)	Survived 56 days (2 pigs)	Dead in 56 days (10 pigs)	Survived 56 days (2 pigs)	Dead in 56 days (8 pigs)	Survived 56 days (9 pigs)
Inguinal nodes	20	1	10	2	8	9
Mesenteric nodes	14		4			2
Other lymph nodes	11	1	6			2
Liver	17	1	6		6	9
Spleen	20	1	10	2	8	9
Lungs	16		3			
Kidney	1					
Diaphragm	10		4			
Intercostal spaces	8		2			
Intestine	2		—	—		
None	—	1	—	—		

TABLE 3. EXPERIMENTAL TUBERCULOSIS IN DIETHYLSTILBESTROL-TREATED AND CONTROL GUINEA PIGS: AVERAGE INCUBATION AND MORTALITY

Treatment	No animals*	No. deaths in 56 days	Mortality	Average incubation	Survived 56 days†
Diethylstilbestrol	5 castrate	3	60.0	31 days	2
	5 intact	4	80.0	29 days	1
None—controls	5 castrate	1	20.0	54 days	4
	6 intact	3	50.0	41 days	3

All females.

All survivors had tuberculosis at autopsy.

h castrate and intact, showed evidence of severe, generalized infection similar to that observed in animals in the previous experiments with alpha-estradiol dipropionate.

#### DISCUSSION

Titration experiments usually consider lethality as an endpoint. A given dose of virus kills all animals injected with it, nor a given dose of a biological or drug

invariably protect all animals against a given dose of virus. On the other hand, an experimental animal injected with a given dose of virus may have received multiples or fractions of the M.L.D. Similar variations are encountered with substances which protect against (or enhance) infection.

The effect of treatment with biologicals or drugs may be reflected in: 1) incubation period, 2) clinical severity, 3) survival, and

TABLE 4. EXPERIMENTAL TUBERCULOSIS IN DIETHYLSTILBESTROL-TREATED AND CONTROL GUINEA PIGS:  
ANATOMICAL DISTRIBUTION OF LESIONS AT AUTOPSY

Site of lesion	Treated with diethylstilbestrol				Untreated controls			
	Dead in 56 days		Survived 56 days		Dead in 56 days		Survived 56 days	
	Castrate (3 pigs)	Normal (4 pigs)	Castrate (2 pigs)	Normal (1 pig)	Castrate (1 pig)	Normal (3 pigs)	Castrate (4 pigs)	Normal (3 pigs)
Inguinal	3	4	2	1	1	3	4	3
Mesentery	3	4	2			1*		
Other lymph	3	3	2	1		1*		
Liver	3	4	2	1	1	3	4	3
Spleen	3	4	2	1	1	3	4	3
Lungs	3	4	2	1		1*	1	
Kidney	1		1					
Diaphragm and intercostal spaces	3	4	2					
Other	1							

All female guinea pigs.

\* This animal resembled the diethylstilbestrol-treated animals at autopsy.

4) mortality. Incubation periods and clinical severity (clinical severity not usually practical in experimental disease) are considered and measured in terms of survival but such measurements do not go beyond the death of the animal. In general, it is difficult to go

beyond this endpoint, but in experimental tuberculosis one can in a sense express mortality in terms of "degree of mortality" judged by the extensiveness of the lesions. From tables 2 and 4 it is evident that there are differences between the treated and

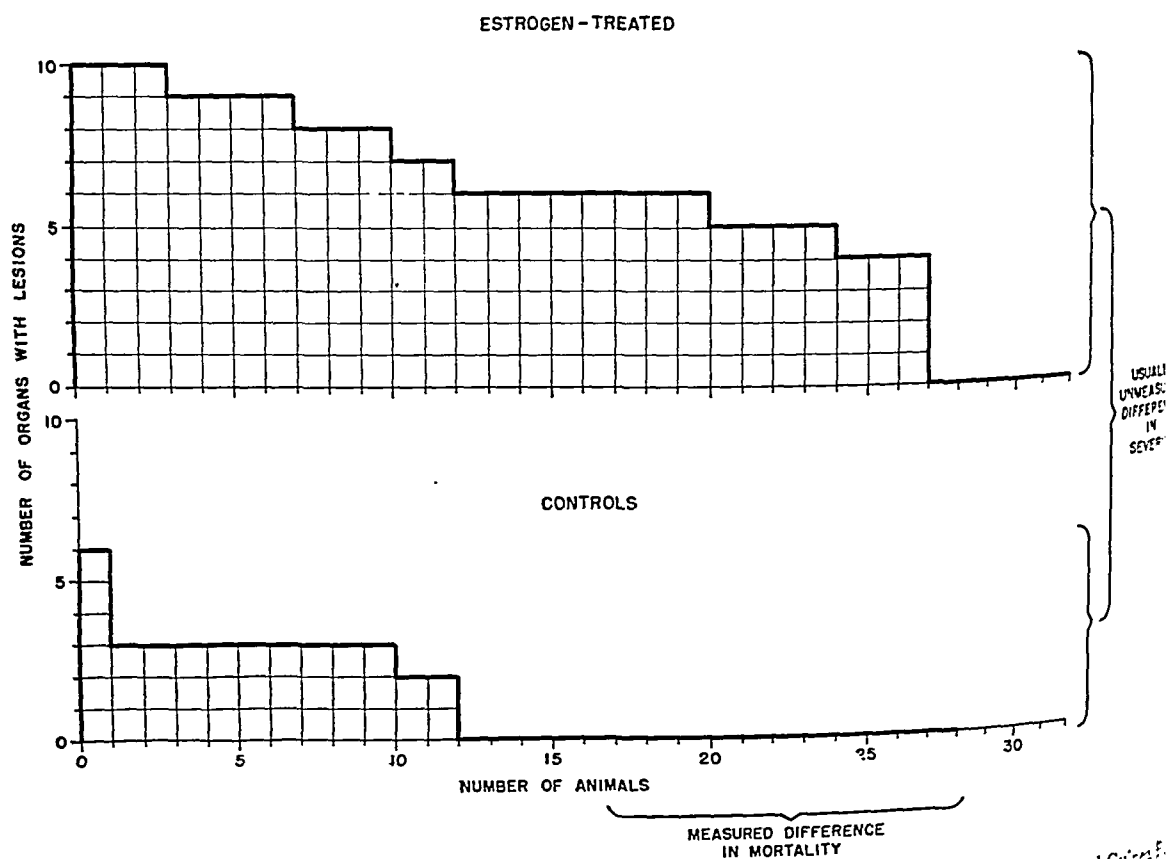


FIG. 2. Comparative Severity of Tuberculosis (number of organs involved) in Estrogen-treated and Control Guinea Pigs.

treated guinea pigs, when fatality is taken as an endpoint, may not necessarily reflect the total differences among the different groups. Aside from the usual measured differences between survival and death, there are not only differences in the "degree of survival" as judged by a comparison of the incubation periods and total survivors, but differences in "degree of mortality" as well. If the extent to which the infection is generalized may be taken as a measure of the degree of mortality," then an estimate of the total effect of treatment should include the "degree of mortality" as measured by the extent of the lesions in the dead animals. In figure 2, both the survival and mortality of all estrogen treated and control guinea pigs, and the extent of the tuberculous lesions in the dead animals are plotted schematically so as to illustrate the differences in the extent of tuberculous infection as judged by the anatomical distribution and frequency of lesions observed at autopsy. Tuberculous lesions were observed in a maximum of 10 organs for the present purpose. This method is conservative since it is based on presence or absence without considering the extent of a tuberculous lesion in a given organ. The quantitative differences in mortality between the estrogen-treated animals and the normal control guinea pigs to infection with the tubercle bacillus is reflected on the vertical axis in figure 2. Such differences usually cannot be read in experimental disease—the usual readable differences being those which appear on the horizontal axis—survival and death, with death as the endpoint.

Attempts to correlate the distribution of lesions with length of survival time indicated that the time of death is not a good measure of the extent of tuberculous lesions. It is not entirely clear why control guinea pigs dying should have on the average much less extensive lesions than estrogen-treated animals dying at the same time. In both the treated and untreated groups guinea pigs dying early in the course of the experiments showed the same "degree of severity" as those surviving for longer periods. However, regardless of

survival time (incubation), the difference in the "degree of severity" between the estrogen-treated and untreated animals was consistent. The imperfect correlation between extent of tuberculous lesions and survival time suggests that in the guinea pig some factor of localization and extent within an organ may be more closely related to the moment of death than the severity of infection as judged by the number of organs involved.

#### SUMMARY

Guinea pigs under treatment with alpha-estradiol dipropionate, testosterone propionate, and diethylstilbestrol in oil, and normal guinea pigs of the same age and sex, were inoculated with sputum from patients with active tuberculosis. The group treated with diethylstilbestrol included both intact and castrated females.

These hormonal preparations induce a decrease of resistance of the animals to experimental tuberculosis. This was shown by three measurable differences in the results of inoculation; *i.e.*, the average intervals between inoculation and death; the total mortality at different times; and the severity of infection as judged by the extent of lesions in the animals.

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# Some Observations on the Use of Thiobarbital as an Antithyroid Agent in the Treatment of Graves' Disease<sup>1</sup>

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THIOURACIL is now extensively employed in the treatment of hyperthyroidism and it is clear that the one drawback to its use is the occasional incidence of serious toxic reactions. Currently it would appear that one out of each hundred treated cases has developed agranulocytosis and as a consequence one in each thousand has died. While this constitutes a low mortality rate for a serious disease especially when compared with the death rate associated with surgical therapy, it would be most desirable further to reduce or to eliminate it. The more common side reaction from thiouracil, drug fever, while not a serious complication in itself usually requires that the drug be discontinued and the disease treated in some other way. As there are, as yet, no specific or certain methods of preventing or treating such drug reactions, the investigation of antithyroid compounds has continued with the aim of finding a substance superior to thiouracil for clinical use. To this end, thiobarbital has been tested in man, and while the results show that the aim has not been achieved the data obtained seem worthy of record.

Thiobarbital (5,5-diethyl-2-thiobarbituric acid) differs from barbital only to the extent that one oxygen atom is replaced by an atom of sulfur. It is only moderately active as a sedative or hypnotic (7), and in common with many other thiobarbiturates large doses in animals exhibit both a depressant

and a stimulating effect upon the nervous system. When surgical anaesthesia is induced the animals retain hyperactive reflexes and appropriate stimuli give rise to convulsive movements. Its property of inhibiting the endocrine function of the thyroid gland seems to be dependent upon the presence of the sulfur atom at position two and upon the two substituents on carbon atom number five. A number of other thiobarbiturates which meet these requirements, including the widely-used intravenous anaesthetic, pentothal, also have antithyroid activity (1), but on the basis of tests in rats thiobarbital is the most active of more than 30 thiobarbituric acid derivatives that have been assayed (4). Its antithyroid activity is manifested by doses which are well below those required to produce sedation. When administered to rats in small doses thiobarbital appears to be somewhat more active than thiouracil and slightly less toxic as judged by the rate of growth. Large doses seem to be less effective but much more toxic than comparable doses of thiouracil (1, 3). The prolonged administration of this and other thiobarbiturates in dogs and in rats has been found to result in no anatomical changes except a fatty infiltration of the liver (12, 3).

## CLINICAL DATA

Observations on the effect of this compound<sup>2</sup> in man have extended over 16 months

<sup>2</sup> Thiobarbital was generously supplied by the Abbott Laboratories, North Chicago, Illinois and the Lederle Laboratories, Inc., Pearl River, New York.

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TABLE 1

Case No.	Age and sex	Initial wt.	Other diagnoses	Dosage Grams/day*	B.M.R.		Complications and toxic effects	Comments
					Initial	Subsequent†		
<b>Hyperthyroidism</b>								
1	52M	126	Thiouracil sensitivity	0.2(40) 0.15(50)	+45	— 1(16)	Died, liver disease—see text	
2	72F	107	Diabetes Pyelonephritis	0.2(29)	+30	+16(28)	Drug fever 4th to 11th day. Died, agranulocytosis—see text	
3	23F	101		1.0(1) 0.2(96) 0.1(69)	+54	+ 8(29)	Early myxedema 4th month	Complete remission‡ 6 months
4	60F	96		1.0(1) 0.2(7) 0(4) 0.2(83) 0(11) 0.2(3)	+33	+ 8(21)	Drug fever 7th to 11th day. Again after intermission	Changed to another compound
5	46F	126	Angina pectoris	1.0(1) 0.3(84) 0.2(56) 0.1(56)	+37	+ 6(28)	None	Complete remission 5 months
6	32F	118	Pregnancy	0.5(1) 0.3(60)	+21	+ 2(41)	None	No cardiac symptoms
7	23F	125		1.0(1) 0.3(85) 0.2(28) 0.1(56)	+34	+18(14)	Early myxedema 4th month	Initial response good—subsequent course unknown
8	50F	91		0.5(1) 0.3(4) 0.2(5) 0(3) 0.2(146) 0.1(93) 0.05(30+)	+77	+33( 9)	Drug fever 8th to 12th day. Early myxedema 6th month	Complete remission 2 months
9	28F	110		0.2(125)	+43	+15(68)	Drug fever second week	
10	55F	103	Congestive heart failure	0.2(13) 0.1(75)	+24		Malaise, headache second week	Changed to another compound at 4 months
11	42F	127		0.2(38)	+10	— 9(76)	None	Complete remission 8 months
12	61F	122		0.2(32)	+43	+21(32)	None	Discontinued because diarrhea uncertain
13	45F	107	Thiouracil sensitivity	0.1(40) 0(16) 0.05(19)			Fever and leukopenia both occasions	Changed to another compound
14	51F	118		0.1(106) 0.05(28) 0.025(28)	+21	— 6(44)	None	Complete remission 3 months
15	54M	160		0.1(72+)			Lobar pneumonia	
16	56F	124		0.1(153+)			None	Good clinical response
17	50M	114		0.1(51+)			None	
18	46M	148	Pretreated with Iodine	0.1(195+)			None	Good clinical response
<b>Hyperthyroidism</b>								
19	47M	123	Auricular fibrillation	0.2(186) 0.1(69) 0(49) 0.1(60+)	+35	+ 6(90)	Early myxedema 6th month	Fibrillation reverted with quinine
20	53M	142	Cholecystitis Arthritis	0.5(1) 0.2(95)	+30	+ 7(80)	None	Inadvertently discontinued—complete remission 8 months
21	58M	121		0.2(28) 0.3(76) 0.2(7) 0.1(28) 0.05(126)	+71	+16(50)	None	Complete remission 2 months
22	74F	120	Congestive heart failure	0.2(182)	+43	+28(70)	None	Complete remission 4 months
23	46F	147	Partial ophthalmoplegia	0.1(40+)	+47		None	Cardiac failure not improved
<b>No Thyroid Diseases</b>								
24	73F	112	Hypertension Angina	0.2(7) 0(11) 0.2(22)			Drug fever both occasions	Not improved
25	54F	91	Rheumatic heart disease; failure	0.4(8) 0.2(105)			Somnolence on larger dose	Not improved
26	59F	134	Myasthenia	0.1(14)			None	Discontinued because diarrhea uncertain
27	46F	103	Hypertensive heart disease	0.2(8)			Lassitude and headache	
28	52F	106	Congestive heart failure	0.5(1) 0.3(8) 0(4) 0.1(4) 0.2(52)			Drug fever 8th to 13th day	Not improved
29	50F	141	Congestive heart failure	0.4(10) 0.2(245)			Somnolence on larger dose	Goiter and myxedema 4 months. Not improved
30	32F	108	Addison's disease	0.3(1) 0.2(5)			None	Discontinued because diarrhea uncertain

\* The figures in parentheses after each dosage are the number of days that the dose was given. The + sign indicates that treatment is still being given.

† The subsequent B.M.R. value is one reading selected to give an index of the rate of response. The figures in parentheses indicate the number of days of treatment before that reading was taken.

‡ By complete remission is meant a continued absence of subjective and objective evidence of hyperthyroidism after therapy was discontinued.

since February, 1944. In all, 30 cases are included in this report, 23 of these being clear instances of hyperthyroidism. The remaining seven patients included four who suffered from advanced cardiac decompensation and three in whom the diagnosis of hyperthyroidism was in doubt. The patients with no evidence of thyroid disease are included for the purpose of better evaluating the incidence of the side effects of the drug.

Five additional patients received thiobarbital for a few days only, and as no metabolic or toxic effects were observed these have been omitted from this report.

The pertinent data illustrating the effectiveness of this compound and its toxic effects are given in table 1. The first 18 patients listed gave no history of recent iodine therapy. The next five had received full doses of iodine up to the time thiobarbital

was begun. The last seven patients are considered to have had no disturbance of thyroid function.

The dosage and duration of treatment is shown in full. With the exception of seven patients who are still under treatment the total duration of therapy is recorded. In almost all cases the medication was given at twelve hour intervals, a few received three doses daily and several were given their total daily dose once each day.

The initial metabolic rate shown in the table usually represented the minimal level reached before therapy was begun but some of the values are averages of the pre-treatment determinations. The one subsequent value shown was selected to show the rate of the metabolic response. All complications and intercurrent events which might possibly have been attributed to the medication are listed in the table. Some of these may not have been side effects of the drug as noted below.

The initial metabolic response in a series of nine selected cases is shown in figure 1 which includes eight patients who had not recently received iodine and who were followed by sufficiently frequent metabolic rate determinations to insure a satisfactory record of the response. It is clear that the metabolic responses are quite as prompt as a similar group of ten patients of comparable severity treated with thiouracil.

Clinical improvement followed the declining metabolic rate and no consistent difference could be detected between this compound and thiouracil as to the rate and degree of symptomatic improvement.

The eventual result of continued treatment was quite as satisfactory as that noted with thiouracil. In eight cases a sustained remission followed when the treatment was discontinued. In one patient (No. 19) a recurrence of the manifestations of hyperthyroidism followed when the drug was withdrawn after eight months of continuous treatment. This man had previously undergone a two stage subtotal thyroidectomy and evidence of hyperthyroidism and auricular fibrillation had been present since his dis-

charge from the army in 1918; the gland was large and nodular. Thiobarbital was discontinued and substituted by another compound in three instances; only in case 4 was this done because of intolerance to the drug.

### Dosage

The dosage used in the first 22 patients was most often 0.1 gm. at 8 or 12 hour

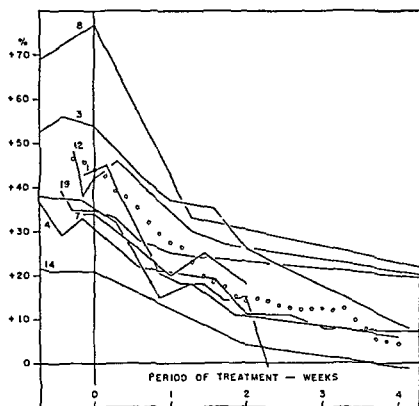


FIG. 1. Rate of decline of the metabolic rate of nine patients with Graves' disease. None except number 19 had recently received iodine. The open circles represent the average rate of response of ten comparable patients treated with thiouracil as previously reported (2).

intervals (0.2 to 0.3 gm. per day), and it was not realized that this dosage was unnecessarily large until an opportunity was provided of observing the results of prolonged treatment. Indeed in seven patients therapy was initiated by the administration of a single dose of 0.5 gm. or a total dose of 1.0 gm. during the first 24 hours. This was done with the aim of achieving an effective concentration in the body promptly. It was later apparent that this only served to increase the already excessive dosage. It may have been a rational procedure had the subsequent dosage been considerably reduced. However three of the six instances of drug fever occurred among the seven patients who received a large priming dose, suggesting that this procedure favors the occurrence of side effects.

When treatment had been continued for several months, evidence of hypothyroidism was observed in a number of patients. It was not until then that the greater effectiveness of this compound was fully realized. Eventually five patients in all were observed to develop definite manifestations of myxedema; this was accompanied by thyroid enlargement, a phenomenon consistently associated with excessive maintenance dos-

## TOXIC EFFECTS

As far as can be determined from the medical literature thiobarbital has never before been administered to man. For this reason all untoward events occurring during the course of therapy in each case have been recorded, and it will be assumed that the drug was directly or indirectly responsible until such time as a wider experience with this compound should show otherwise.

### *Sedative effect*

When one half or one gram was given as a single dose or in divided doses over the course of the first day noticeable drowsiness or somnolence followed in five of seven cases usually on the day after. The two cases given 0.4 gm. daily became most uncomfortably somnolent after five to seven days of therapy. Two out of six cases receiving 0.3 gm. daily complained of lassitude and drowsiness after a week had passed. The daily administration of 0.2 gm. was not followed by a noticeable sedative effect in any of 20 cases. Clearly these side effects were due to the drug and were to be anticipated from its known hypnotic properties, indeed in some instances the larger doses were given deliberately in order to estimate the dosage which would have a sedative effect in man. It is perhaps significant that the patients usually complained of the drowsiness as if the sensation was an unpleasant one.

### *Drug fever*

A definite febrile response, in all probability related to the administration of thiobarbital, occurred in six patients. The fever began on the fifth to eighth day of treatment, increased slowly in intensity until a body temperature of 102° to 105° F. was reached and then declined; (fig. 2) the febrile period lasted for as long as seven days even though the drug were immediately withdrawn. Probably malaise accompanied the fever and usually there were pains in the muscles especially those of the neck, shoulders and back. No skin eruptions, lymph gland enlargement or edema were observed. The leukocyte count remained normal or was slightly elevated.

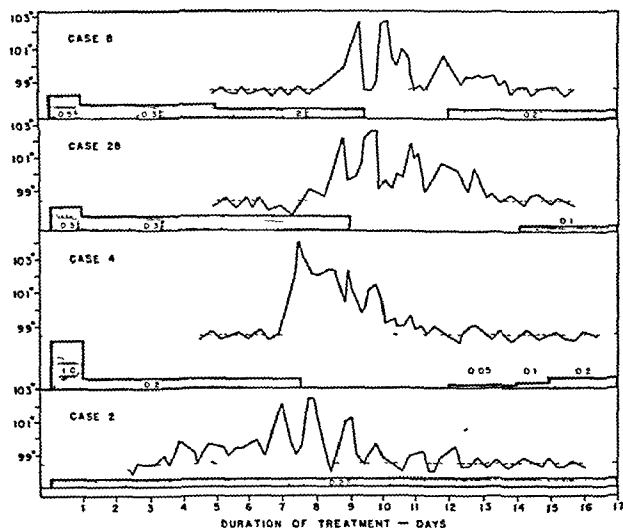


FIG. 2. Temperature charts of four patients who exhibited a febrile response when treated with thiobarbital. The base line in each case is at 98.6°F. The temperatures during the period of elevation were taken rectally except in case 2. The dosages of thiobarbital are shown by the shaded areas.

age. The doses which proved to be excessive for maintenance were 0.1 gm. twice daily in four and 0.1 gm. once daily in one. In two of the former cases a dosage of 50 mg. twice daily was also found to be excessive, while at the other extreme in only one case (No. 19) was a dose of 0.1 gm. once daily found to be inadequate; when 50 mg. twice daily was substituted in this instance, adequate maintenance was achieved.

The last eight cases to be treated received only 0.1 gm. daily; in three of them the dose was given once daily, in the others it was divided and given at 12 hour intervals. Each of these cases has responded in a satisfactory manner. It may be significant that only one toxic reaction (case 13) was observed among these eight cases and this was not proved to be caused by the drug.

and the granulocyte percentage was within the upper region of normal. When the fever had subsided the drug was readministered without evoking a second febrile response. This course of events was so different from that observed in drug fever from thiouracil that three cases were observed before it was clear that the drug was responsible for the fever. Indeed two cases continued to receive the drug throughout the course of the fever and in these the duration of the fever was not appreciably prolonged. In four cases thiobarbital was continued for periods of two, three, four and ten months respectively after the febrile episode without further manifestations of toxicity or sensitivity. In case 4, however, readministration of thiobarbital after a brief intermission at the end of three months' therapy evoked a second febrile response, and case 24 continued to run a slight fever when the drug was continued after the acute febrile episode had passed.

A seventh patient (case 13) experienced three mild febrile illnesses, one while receiving thiouracil and two while taking thiobarbital. Each was accompanied by leukopenia and no organic disease or localizing signs of infection could be found. There was no constant relationship between the time of onset of these disorders and the duration of treatment and the medications cannot with certainty be incriminated. Two patients (cases 10 and 27) experienced malaise, lassitude and headache without fever during the second week. It is possible that these patients experienced a reaction similar in kind to drug fever, but of such mild degree as not to disturb temperature regulation. They are of especial interest in possibly pointing to an explanation of the febrile response. As noted above, the larger daily doses often gave rise to somnolence and lassitude after a week of treatment indicating a cumulative effect maximal at that time. Perhaps the mild constitutional reactions and the fevers which occurred during the second week of treatment are also indications of an excessive accumulation of thiobarbital or of one of its degradation products in the body.

Two patients in this series died while taking thiobarbital, one of rapidly progressive liver disease and one of agranulocytosis. The details of these two cases were as follows:

*Case 1.* A man of 52, having a typical case of Graves' disease of six months' duration with minimal ocular signs and slight thyroid enlargement, was treated with thiouracil beginning on June 1, 1943. Response of treatment was prompt and the disease was satisfactorily controlled for about three months. Thereafter the patient refused to attend the out-patient clinic regularly and discontinued the medication on several occasions; hyperthyroidism returned. During the nine months of intermittent thiouracil treatment the patient suffered from pharyngitis, was subjected to tonsillectomy in another hospital, and experienced several episodes of ill health the nature of which was not determined. Finally he concluded that the drug caused him to be unwell, and he refused to take it any longer. In view of the severity of the hyperthyroidism and the previous difficulties in managing this patient at home he was admitted to the hospital for treatment with thiobarbital which was given in a dose of 50 mg. every six hours (0.2 gm. daily). The basal metabolic rate fell from +45% to -1% in 16 days and remained normal after the dosage was reduced to 50 mg. three times daily on the 30th day of treatment. The body weight increased from 126 pounds to 153 pounds in two months and the patient had resumed work as a day laborer. Just three months after thiobarbital was started, there developed malaise, weakness, loss of appetite and marked fatigue. Two days later the urine was noted to be dark and the stools light in color, and after two more days the skin became noticeably yellow and he entered the hospital for the third time. Medication was discontinued on the day before admission.

There was deep jaundice, the liver to palpation appeared to be greatly enlarged though it was of normal size on x-ray examination. The urine contained bile and urobilinogen; the feces were light brown. Detailed clinical and laboratory examinations failed to establish a definite diagnosis. The jaundice deepened and the patient died in coma on the eighth hospital day. A post mortem examination was not permitted.

*Case 2.* A woman of 72 years was admitted to the hospital in diabetic coma. She was not previously known to have suffered from diabetes but after recovery from coma there persisted a severe diabetes which was difficult to regulate with large doses of insulin. Because of persistent pyuria and low grade fever a diagnosis of pyelonephritis was made and sulfadiazine was administered in full dosage for nine days. During convalescence a number of features suggested the coexistence of thyrotoxicosis, the pa-

tient was alert and active, the skin was warm and moist and the eyes were bright and the palpebral fissures wide. The pulse rate was usually over 100 beats per minute at rest and the basal metabolic rate was found to be +30 and +35 on three tests.

Thiobarbital was given in a dose of 0.1 gm. every twelve hours. During the sixth to tenth days of treatment there was a return of fever (see fig. 2) which subsided even though the drug was not withdrawn; this was interpreted as drug fever though the possibility that it was a further manifestation of pyelonephritis could not be excluded. During the fourth week of treatment the patient complained of weakness and lassitude and the temperature was elevated in the evenings to 99° to 100.5°F. On the 29th day the total leukocyte count which previously had varied between 5,700 and 9,400 was found to be 750 and no granulocytes could be found in the smear. Thiobarbital was discontinued and treatment with penicillin, increased dosage of vitamins, crude and purified liver extract and pentnucleotide was instituted at once. For four days the patient showed no localizing evidence of infection and the temperature reached maximal levels of 101° to 102.8°F. Because of a mild anemia which had been noted since admission a transfusion was given on the fifth day of the disease; this was promptly followed by a chill and the temperature rose to 105.6°F. During the next two days the high fever continued and the patient died eight days after the diagnosis of agranulocytosis was made. On the day of death *E. coli* was grown from the blood and at post mortem examination an abscess was found in the sternum at the site of three aspiration biopsies of the sternal marrow. Other medications given during the course of thiobarbital therapy were insulin, various vitamin preparations, digitalis, aspirin, whisky and phenobarbital. There was no evidence that the various forms of treatment directed toward a stimulation of granulopoiesis were of any benefit. The total leukocyte count varied between 600 and 1600, and no granulocytes appeared during the eight days.

#### DISCUSSION

These studies serve to show that thiobarbital is more active gram for gram than thiouracil in inhibiting thyroid function in man. Given at eight or twelve hour intervals the minimal initial dosage of thiouracil which will control the majority if not all cases of hyperthyroidism has proven to be 0.4 gm. daily though 0.2 gm. has been sufficient in some cases. In the present study 0.2 gm. of thiobarbital has not failed to be effective and 0.1 gm. was adequate in all eight instances. Thus it would seem that thiobarbital is a little more than twice as effective as thiouracil. The average maintenance dose of thiouracil is

0.2 gm. daily in two doses at 12 hour intervals while these studies indicate that the maintenance dose of thiobarbital averages 0.1 gm. daily or somewhat less. This again would indicate that thiobarbital is more than twice as active as thiouracil.

The data also show that a single oral dose of thiobarbital has a more prolonged action than a single dose of thiouracil. It is now well recognized that the effectiveness of thiouracil is greatly diminished if the doses are spaced at 24 hour intervals instead of at eight or twelve hours (2). Thiobarbital on the other hand has been quite effective even when only one dose is given per day. In several instances, however, there was an opportunity to observe that a dose of 50 mg. every twelve hours was distinctly more effective than a single daily dose of 100 mg.

Although a fairly good approximation of the minimal effective dose of thiobarbital can be obtained from this small series of cases, the data are entirely inadequate to permit an analysis of its toxic effects. In this series there was a very high incidence of side effects, but there is some uncertainty as to whether all of them were caused by the drug. Some of them, however, were probably toxic effects and the result of excessive dosage. As this compound seems to be degraded or eliminated at a slow rate, at least at a rate slower than that of thiouracil, its effects would tend to be cumulative. This possibility receives support from the observation that several patients began to be drowsy only several days or a week after starting to take the compound in a dose of 0.3 or 0.4 gm. daily. Perhaps the high incidence of drug fever was in part due to this cumulative quality and if so it would seem reasonable to expect that it would be less likely to occur if the minimal effective dosage were not exceeded. Furthermore the febrile response appears to be entirely benign and the drug can usually be continued; in the case of thiouracil a febrile response usually precludes further therapy with that compound.

It is not known whether the fatal liver disorder in case 1 was caused by the thiobarbital or not. The animal experiments

(2) showing that accumulation of fat in the liver follows the prolonged administration of thiobarbiturates suggests that thiobarbital might cause liver damage in man. However, none of the other treated patients showed any evidence of impaired liver function and it is well known that infectious hepatitis can give rise to a syndrome clinically indistinguishable from that observed in this patient. The agranulocytic reaction (case 2) can with more assurance be attributed to the thiobarbital therapy. The analogy with thiouracil is most suggestive; the agranulocytosis was detected on the 29th day of treatment and the case was complicated by infection and diabetes, features which have commonly been associated with the agranulocytoses caused by thiouracil.

In spite of this most unfavorable record this compound would appear to be of value in the treatment of hyperthyroidism and to deserve further study. Used in the proper dosage and with due consideration of the toxic effects to be anticipated, more favorable results should be obtained. Also a small series of cases such as this can give a very true picture of the real nature of a substance. For example, the experience with thiouracil in the series published from different clinics has been most divergent as to the incidence of toxic effects. Some reports show an unusually high incidence of serious complications; for example, Lozinski and Minovitch (8) recorded one death from granulocytosis among five treated cases and Evans and Flink (6) encountered five serious toxic reactions among 26 cases. On the other hand no serious toxic reactions were seen in series of 100 cases reported by Palmer (11), 43 by Montague and Wilson (9), 34 by Newman (10) and more than 40 by Eaton (5).

It would appear that an appropriate dose of thiobarbital would be 50 mg. every twelve hours for the initial period of therapy in cases of the usual severity. It is possible that a somewhat smaller dose could be used in mild cases which would not be endangered should the dose prove to be inadequate. On the basis of the findings to date it would appear to be

unwise to give thiobarbital in dosages of 0.2 gm. daily or higher. While a single dose in 24 hours has been effective in some instances it would seem reasonable to take advantage of the apparently greater effectiveness of the compound when it is given every twelve hours.

#### SUMMARY

The effectiveness of thiobarbital in the treatment of hyperthyroidism and its toxic effects have been studied in 30 cases given total daily doses of from 0.1 to 0.4 gm. All of the manifestations of hyperthyroidism were satisfactorily controlled, but in the dosage used there was a high incidence of complications. Two deaths occurred, one from agranulocytosis and one from an acute liver disorder; six cases experienced a febrile reaction during the second week of treatment, but this did not preclude continued treatment. It is estimated that thiobarbital is more than twice as active as thiouracil in inhibiting the function of the thyroid gland in man, and that it is more toxic than thiouracil when the minimal effective dose is exceeded.

#### ACKNOWLEDGEMENT

This study was made possible by the generous cooperation and help of the members of the resident and visiting staffs of the Peter Bent Brigham Hospital. We are especially indebted to Dr. A. W. Cantratto for permission to include five of his private patients (cases 15, 16, 17, 18, and 23) to Dr. J. F. Fay for permission to include case 13, and to Drs. J. F. Marchand, R. Macquigg, A. Roos, B. E. Lowenstein, and W. P. VanderLaan for their assistance in carrying out this study.

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# LETTER TO THE EDITOR

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## THE USE OF GLUCOSE IN THE TREATMENT OF DIABETIC COMA

IN DIABETIC COMA the essential disturbance is the relative or absolute lack of insulin. It is a deficiency state in which the primary problems are the estimation of the amount of insulin required and its prompt administration the first few hours of treatment. As the result of the hyperglycemia, polyuria and ketosis one finds secondary changes, such as extreme dehydration and loss of base, chiefly sodium; both are lost from intra- and extra-cellular spaces. These latter changes must be treated by the simultaneous administration of adequate amounts of water and salt. When a sufficient quantity of insulin has been given to provide a reserve making possible the normal utilization of carbohydrate, food including protein as well as carbohydrate is needed. Much confusion at present exists because of differences of opinion regarding the use of glucose by intravenous or subcutaneous administration during diabetic coma.

Possibly an overemphasis of the importance of an immediate restoration of glycogen stores in the liver is a factor in this confusion. Non-diabetic ketosis, as in starvation, pregnancy, etc., never leads to a condition clinically comparable with diabetic coma. The development of ketosis in diabetic coma is accompanied by progressive hyperglycemia. Presumably the excessive rise in sugar in the blood is due to the lack of insulin and the increasing glycogenolysis in the liver and muscles. At the height of diabetic coma the liver is usually considered to be almost devoid of glycogen. In starvation and hyperthyroidism the liver glycogen is also reduced without impairment of glucose oxidation. Indeed it has long been known that in diabetes, the starvation treatment of Allen, which certainly reduced liver glycogen, was accompanied by a rising respiratory quotient and an increase in carbohydrate utilization. There is no proof or the supposition that oxidation of glucose is

prevented by absence of glycogen in the liver or that it is improved by increasing liver glycogen *per se*. However, in diabetic coma in the absence of sufficient insulin carbohydrate yields to fat as the chief substrate for oxidation in the liver. The production of ketone bodies in the liver therefore mounts steadily and exceeds the capacity of the tissues to oxidize or of the kidneys to excrete them. This is not due to a lack of available carbohydrate.

The table of the approximate carbohydrate content of human tissues given by Root<sup>4</sup> shows that when the blood sugar in diabetic coma is within the range of from 500 to 700 milligrams per 100 cc., there may be already present in the body fluids excessive glucose in an amount varying from 100 to 146 grams, because of the inability of the body to utilize it. Under these circumstances, if glucose is given intravenously to a patient in diabetic coma, the respiratory quotient does not rise above the level for fat as shown by Root and Carpenter.<sup>5</sup> Glucose administered without insulin to a patient in diabetic coma, having a CO<sub>2</sub> content of the blood below 20 volumes per cent, merely accelerates the downward course and may soon be followed by hyperglycemia, further dehydration, anuria and pancreatic exhaustion. The essential problem is to find the dose of insulin which will bring about oxidation of glucose so that the oxidation of fat and the consequent formation of ketone bodies may be reduced. The problem is difficult because with severe diabetic acidosis insulin resistance increases so that the insulin requirement may vary from 100 to 1,000 units.

The simultaneous administration of glucose with salt and water has been advised by Soskin and Levine<sup>6</sup> and by Butler.<sup>2</sup> These authors consider that the stores of glycogen in diabetic coma are negligible, and they hold that the sugar present in the blood and intercellular fluid is inadequate to replenish the stores of glycogen. The case discussed by Butler gives a clear picture of the effect of giving glucose to a



child who was improving with adequate insulin treatment. The note describes the immediate return of glycosuria and acetonuria together with the fact that the patient became less responsive and respirations assumed a peculiar gasping quality. Repeatedly such unfavorable events have followed the administration of glucose in serious diabetic coma. Actually, Mirsky,<sup>3</sup> who studied the effect upon diabetes of the administration of large amounts of carbohydrate (500 grams or more in 24-hours), specifically warned against such therapy because of the danger of pancreatic exhaustion.

The danger involved in the administration of glucose depends upon the amount of glucose administered and the rate at which it is given. The continuous injection of glucose at a rate in excess of caloric needs leads to death even in normal animals. Astwood<sup>1</sup> gave glucose solution to a normal dog at the rate of 1.7 grams per kilogram weight per hour, and death resulted at the end of 70 hours. Those dogs received seven calories in the form of glucose each hour, yet their metabolic needs were only two calories per hour. A diabetic boy in coma has a total metabolism of about 70 calories per hour. If he is given 1,000 cc. of 10 per cent glucose solution in an hour's time he has received 400 calories or approximately six times his caloric need in that form. In one fatal case, that of a 19 year old boy, 350 grams of glucose had been given in a few hours without adequate insulin. At present one of the chief errors and causes of death in coma cases is the overfeeding of such patients with excessive amounts of glucose—amounts per hour greater than the caloric needs.

No one supposes that in coma the administration of glucose at the rate of perhaps 10 grams per hour would be harmful, provided a sufficient amount of insulin had been given to make possible its normal utilization. Clinical results cannot be disregarded in a field of such complexity. At the Deaconess Hospital<sup>4</sup> no glucose has been given to patients actually in diabetic coma

since 1923. In 123 consecutive cases of diabetic coma where the blood CO<sub>2</sub> content was volumes or less treated between August 19 and May 1, 1944 only two deaths occurred at a rate of 1.6 per cent. Even those deaths could have been prevented by earlier admission to the hospital of one case and the omission of the large amounts of glucose given in the early treatment of the other. The low mortality was attributed to the more prompt use of large amounts of insulin. Thus, during the first three hours after admission to the hospital the average patient received 216 units of insulin; in that group were included certain profoundly unconscious patients, with blood sugar values from 500 to 1400 milligrams, who received as much as 500 units in the first three hours. A reduction in the total metabolic rate is achieved by rest in bed and the avoidance of overfeeding. After recovery from the acute stage, a diet while the patient is in bed providing approximately 15 calories per kilogram of body weight and 150 grams carbohydrate per twenty-four hours should be resumed. Carbohydrate stores are thus gradually replenished.

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HOWARD ROOT, M. D.



# CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. Collaborators: F. A. DE LA BALZE, ISRAEL BRAM, CLARENCE D. DAVIS, ANNA FORBES, URRAY B. GORDON, E. C. HAMBLIN, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO-EMBRIVES, A. E. MEYER, E. C. REIFENSTEIN, JR., LEO T. SAMUELS, HAROLD WOOSTER, AND J. ZANARTU.

## ADRENALS

PRATT, J. P. AND R. L. SCHAEFER.

Sex precocity, virilism, adrenal cortical tumor. *Am. J. Obst. & Gynec.*, (5): 623-633, (1945).

The authors reported three female patients with varying degrees of virilism. One, a thirty-three month old child with marked signs of virilism, had an encapsulated tumor in the right adrenal which was removed. There was a marked reversal to that of a normal child postoperatively and six years later there was no sign of metastasis. The second presented signs of virilism at four months which increased until her death at the age of 25 months. The virilism appeared as a consequence of metastases of a fibrosarcoma of the cheek to the adrenal cortex. The third patient, eight years and four months of age, had only moderate enlargement of the clitoris, no change in voice and lacked increased statural growth. Adrenal tumor was suspected, but operation revealed no adrenal enlargement. —C.D.D.

## ENDOCRINE GENERAL

CHRISTY, C. J.

Vitamin E in menopause. *Am. J. Obst. Gynec.* 50 (1): 84-87 (1945).

The author presented a preliminary report of the clinical use of vitamin E in the treatment of the menopausal syndrome. Twenty-five patients were treated with 10 to 20 milligrams of vitamin E orally, daily over periods of from one to three weeks. Seven reported complete relief, 16 very marked relief and two no relief. There were no undesirable side reactions.

The relief of subjective symptoms coincident with the administration of vitamin E could not be distinguished from that obtained with the natural or synthetic estrogens. The chief advantage of the former was that it was free of any stimulative effect on the breast parenchyma or the genital system. The author stated

that in some patients vitamin E seemed more effective in relieving vasomotor instability symptoms than estrogens.—C.D.D.

CINBERG, B. L.

Postmenopausal pruritis vulvae. *Am. J. Obst. & Gynec.* 49 (5): 647-657 (1945).

The author reported the successful treatment of 14 patients with severe postmenopausal pruritis vulvae in which pretherapy and posttherapy vulval biopsies were obtained. The best method of obtaining relief was to protect the skin from further irritation by the constant application of a bland ointment for at least three months. The author advised the local use of an androgenic ointment (two milligrams of testosterone propionate to a gram of ointment) when there was severe vulval atrophy.—C.D.D.

DE LA BALZE, F. A.

Gynecomastia. *Rev. méd.-quir. de pat. fem.* 21: 309 (1943).

The author reviews the cases of gynecomastia in the literature to 1943, and gives 400 references. He reports additional cases, (1) that of a patient with Addison's disease in whom transitory gynecomastia appeared after the administration of adrenal cortical extract and also after the administration of desoxycorticosterone acetate; in both instances the gynecomastia subsided after treatment was discontinued, (2) that of a patient in whom gynecomastia and hyperthyroidism appeared simultaneously and (3) that of a patient in whom gynecomastia appeared during the development of bronchial carcinoma. The author presents an etiological classification of cases of gynecomastia. He emphasizes two factors in the pathogenesis of this condition (1) the predisposing or chromosomal factors (i.e., the "zygotic make-up" of the individual); this can also be called "potential local feminization" or intersexuality localized in the breast, and (2) the factor which induces the appearance of gynecomastia in the breast prepared by factor

(1); this factor is usually an alteration in the kind or the amount of steroid in the body fluids (in most cases this factor is an excess of estrogens).—*F.A. de la B.*

HAC, L. R., H. C. HESSELTINE, F. L. ADAIR and M. B. CRUDIN

Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis. *Am. J. Obst. & Gynec.* 50 (1): 88-95 (1945).

Of 135 children treated with sulfanilamide, sulfapyridine or sulfathiazole, 89 percent responded satisfactorily to sulfapyridine or sulfathiazole. Sulfanilamide is definitely contraindicated because of a higher percentage of failures and because it tended to produce sulf-resistant strains of gonococci. Diethylstilbestrol was found useful in the treatment of sulfonamide resistant patients.—*C.D.D.*

LEFF M.

The comparative action of posterior pituitary and ergonovine in the third and fourth stages of labor: Observations based on 5000 deliveries. *Am. J. Obst. & Gynec.* 49 (6): 734-738 (1945).

Ergonovine was given intravenously or intramuscularly as soon as the placenta was expressed in 2500 deliveries. Despite firm contraction of the uterus, bleeding occurred and frequently persisted. Much better results have been obtained in a subsequent series of 2500 deliveries by the use of pituitary extract immediately after the placenta was delivered and the postponing of ergonovine injection for 20 minutes.

The better results with the combined therapy was believed due to the fact that posterior pituitary substances cause both contraction and retraction of the uterus and produce retraction of the cervix whereas ergonovine causes a tonic contraction of the uterus but no retraction.—*C.D.D.*

QUIGLEY, J. K.

Habitual abortion. *Am. J. Obst. & Gynec.* 49 (5): 633-641 (1945).

The author reported that 28 of 30 women who had had one or more previous spontaneous abortions went to full term or near it and gave birth to normal children when treated by the usual conservative measures and intramuscular progesterin, five units every four days. The author advised painstaking investigation of

both husband and wife before pregnancy was attempted.—*C.D.D.*

RAICES, A. E., E. B. DEL CASTILLO AND J. GAMBIN.

The 17-ketosteroids in virilization of the adult woman. *Medicina, Buenos Aires* 5: 1 (1945).

The urinary 17-ketosteroid excretion was determined on 75 virilized women. In 26 patients the values were normal; in 49 the values were above the normal level, and in 22 of these the excretion was greater than 30 mg. per 24 hours. In one case of adrenal hyperplasia the values were low (4.8 and 3.2 mg. per 24 hr.), and in one case of adrenal tumor the values were normal (12.3, 9.3, and 6.3 mg. per 24 hr.). A high level of excretion was found in patient without any manifestations of adrenal hyperplasia or tumor. Discrepancies in the 17-ketosteroid excretion of several other patients are discussed. The authors conclude that in adult women with virilization the urinary 17-ketosteroid levels may be normal although elevated values are usually present.—*F.A. de la B.*

SHUTE, W. AND E. SHUTE

The effect of dihydrotachysterol on certain toxemias of late pregnancy. *Surg., Gynec. & Obst.* 81: 83-92 (1945).

The effect of combined dihydrotachysterol and calcium therapy on a series of 42 cases of toxemia of late pregnancy was studied. Four of the patients were of the low estrogen or true preeclamptic type and 38 were of the high estrogen type. The therapy proved ineffective in the true preeclamptic group but was thought to have benefited 42 percent of the high estrogen group. The improvement was manifested chiefly in a lowering of blood pressure. Edema and albuminuria were little affected.—*J.M.*

## GONADS

DEL CASTILLO, E. B., AND C. GALLI-MAININI  
Metrotrophic action of testosterone. *Medicina Buenos Aires*. 5: 144 (1945).

The author reports two cases of dwarfism with infantilism in which menstruation was induced by the administration of testosterone. The actions of sexual steroids on the endometrium are analyzed and the metrotrophic action of testosterone is discussed. The authors conclude that there is a "critical level" in the concentration of the sexual steroids above which

menstruation is inhibited and below which menstruation occurs.—*F.A. de la B.*

JAMAN, J. O.

Exercises in dysmenorrhea. *Am. J. Obst. & Gynec.* 49 (6): 755-761 (1945).

The author treated by exercises 129 women who complained of severe dysmenorrhea, 84 of the primary type and 45 of the secondary type. He reported that 84.5 percent of the entire group and 89.3 percent of the primary type group had definite relief. In many instances this lasted for at least 24 months which was the limit of the follow-up.—*C.D.D.*

LARDING, F. E.

The treatment of functional dysmenorrhea with pregnenolone. *Am. J. Obst. & Gynec.* 50 (1): 56-63 (1945).

Pregnenolone, in doses varying from five to 15 milligrams orally daily, was administered to 83 patients with functional dysmenorrhea. Treatment was started from the fourteenth to the twenty fourth day and continued until bleeding began or the pain lessened. There was satisfactory improvement (50 percent or better) in 60 patients. There was a tendency for the pregnenolone to cause the bleeding to appear early but this was prevented by starting the treatment late in the cycle. There were no other consistent changes in the menstrual cycle. Twenty patients were given progesterone, five to 15 milligrams, intramuscularly during the actual time of the severe pain. The results were disappointing as very little relief was obtained.—*C.D.D.*

ARNACKY, K. J.

Possible use of kymographic tracing instead of endometrial biopsy for the determination of ovulation. *West. J. Surg.* 53: 237-243 (1945).

For the speedy determination of the type of contractions occurring in the uterus, the author describes the following technique: a small uterine cannula covered with a small collapsed balloon is inserted through the cervical canal into the uterine cavity. The cannula is attached to a kymographic writing needle by a rubber tube. With the kymograph in operation, the pressure is slowly increased to 80 millimeters of mercury. The tracing obtained after five to ten minutes will indicate whether the uterine contractions are of the "resting or estrogenic" type or of the progesterone type. The test for pro-

gesterone waves may be done: (1) Seven to ten days before the expected date of menstruation (2) On any day of menstruation or uterine bleeding (3) One to 3 days after the end of menstruation or uterine bleeding. The accuracy of the method was tested by correlating the tracings with endometrial biopsies in 200 patients. One hundred and seventy-six who gave secretory tracings had secretory endometria. Twenty-four had small tracings, called estrogenic or no tracings at all. They all had proliferative endometria with or without dilated glands. Acute vaginitis, cervicitis, endometritis, salpingitis, incomplete abortions, pregnancy and malignancy were considered contraindications to the use of the method. No complications have resulted from 1227 consecutive determinations. The procedure is less painful than endometrial biopsy.—*J.M.*

WEINBERG, C. H.

Essential dysmenorrhea. Its treatment with pavarine. *Am. J. Obst. & Gynec.* 50 (1): 98-101 (1945).

In a series of 100 patients with essential dysmenorrhea, 48 had complete relief and 42 needed in addition only mild sedation when treated with pavarine. This was given three times daily, beginning three days before the expected period and was continued through the first day of bleeding. This drug possesses both musculotropic and neurotrophic action but is not a narcotic like morphine, which action it simulates.—*C.D.D.*

## THYROID

BARTELS, E. C.

Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism. *Ann. Int. Med.* 22: 365-372 (1945).

Sixty-four patients with severe hyperthyroidism have been prepared for operation with thiouracil at the Lahey Clinic since the report issued in May 1944. Fifty of these patients had primary hyperthyroidism and 14 had adenomatous goiter with hyperthyroidism. The disease was considered to be severe in these patients because of their being in the older age group, because of the long duration of the disease and high basal metabolic rates. In 15 of the patients, thyrotoxicosis was complicated by auricular fibrillation or cardiac failure. Thiouracil was administered in a daily dosage of 0.6 gm. When the basal metabolic rate approached +20%,

iodine was added and the two drugs given simultaneously for three weeks. The involution effected by iodine was adequate to overcome the technical operative difficulties experienced with the highly vascular glands resulting from therapy with thiouracil alone. Thiouracil was discontinued one week prior to operation. All patients except those in cardiac failure were treated at home and returned to the clinic every two or three weeks for examination and differential white blood counts. Patients in cardiac failure were hospitalized until compensation was restored. Subtotal thyroidectomy was performed in 52 cases and hemithyroidectomy in 12. Patients in whom thiouracil was given long enough to lower the BMR to normal experienced a smooth anesthesia and negligible postoperative thermal response as compared with iodine-treated patients. The records of two patients who were operated upon before thiouracil had lowered the BMR to normal are presented. These patients had such an unsatisfactory operative course that hemithyroidectomy only was performed and despite this precaution severe postoperative reactions occurred. Patients not previously treated with iodine exhibited approximately one per cent decline in the BMR per day of treatment with thiouracil. Out of a grand total of 119 patients treated with thiouracil, eight displayed toxic reactions consisting of: (a) skin eruption, 1; (b) febrile reaction, 4; (c) leukopenia, 3. All of the reactions disappeared on discontinuance of the drug, although one patient was in the early stages of agranulocytic angina. The author concludes that thiouracil is of great value in the preoperative management of patients with severe hyperthyroidism, in that it greatly reduces the risk of surgical treatment.—*J.M.*

BEARDWOOD, J. T., JR., AND D. C. LEVINSON

Thiouracil in the medical management of hyperthyroidism. *Pennsylvania M. J.* 48: 212 (1944).

In 18 of 20 cases of thyrotoxicosis, thiouracil restored the BMR to normal, with clinical remission and weight gain. Maintenance dosage over several months is better than intermittent treatment. An initial dose of 0.6 gm. daily is recommended. Serum cholesterol, urinary creatinine determinations and galactose thyroid function tests were made. The action of thiouracil is believed to be specific, interfering directly with the synthesis of thyroxine.—*Courtesy Biol. Absts.*

DOBYNS, B. M.

The influence of thyroidectomy on the prominence of the eyes in the guinea pig and man. *Surg., Gyn., & Obst.* 80: 526-533 (1945).

Changes in the prominence of the eyes of patients and 13 guinea pigs after thyroidectomy have been studied. The Hurler exthalmometer was employed for measuring eye changes in patients. Two ingenious devices of the author's design, a caliper instrument and a modified camera lucida, were used to make responding measurements in the animals. Increase in prominence of the eyes of both patients and experimental animals was found. Patients who had adenomatous goiter with hyperthyroidism or exophthalmic goiter developed greater increase in prominence post-operatively than did patients who had adenomatous goiter without hyperthyroidism. Patients whose metabolic rates fell only slightly after operation were inclined to relatively slight increase in prominence of the eyes, whereas those whose rates fell markedly showed a relatively greater increase in prominence of the eyes.—*J.M.*

EATON, JAMES C.

Treatment of thyrotoxicosis with thiouracil. *Lancet* 248: 171 (1945).

Thirty-six cases of thyrotoxicosis were treated with thiouracil, twenty-five of which were observed for at least six months. Included were 4 with toxic adenoma, 4 recurring after thyroidectomy, 4 diabetics and 2 during pregnancy. The maximum dose was 800 mg. daily with 200 mg. as a maintenance dose. Seven cases have remained well after treatment though the drug was not given for periods of three and one-half to eight months. Others had to continue the drug for a year. One case showed granulocytopenia without symptoms which was relieved by cessation of the drug. The thyrotoxicosis was relieved in the pregnant women but one child was born with an enlarged thyroid. Three diabetics in which the diabetes was primary responded well to thiouracil. In one in which the hyperthyroidism was primary, thiouracil was the only patient who failed to respond. Exophthalmus was not appreciably affected. The changes in the size of the thyroid were similar with the mean circumference of the thyroid showing no significant change. Charts of the change in BMR, pulse rate, pulse pressure, body weight and white cell count are given.—*L.T.S.*

WOLDSMITH, E. D., A. S. GORDON AND H. A. CHARIPPER

An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat. *Am. J. Obst. & Gynec.* 49: 197 (1945).

At intervals of 0 to 22 days prior to parturition, pregnant rats were placed on a laboratory diet containing 0.5 per cent thiourea. This resulted in activation and hyperplasia of the thyroid gland and retarded growth of the offspring. A return to a normal diet was marked by return to normal growth and physiological activity. The authors advise caution in the use of thiourea and thiouracil therapy in pregnancy complicated by hyperthyroidism.—C.D.D.

AINES, S. F., AND F. R. KEATING, JR.

Unusual reactions following the use of thiouracil. *J. Lab. & Clin. Med.* 30: 354 (1945).

Two individuals developed unusual reactions to thiouracil which the authors attributed to a toxic disturbance of the central nervous system. Both patients were confused, somnolent and developed myoclonic contractures of various muscles. After complete subsidence, this unusual response was reproduced in each instance, by resumption of the drug. However, one of the two patients had a similar reaction to the "administration of an inert substance." Therefore the nature of the reaction in association with thiouracil therapy still remains in doubt.—T.H.McG.

OUSSAY, B. A.

Thyroid and diabetes. *Semana méd. Tomo Cincuentenario.* 1: 255(1944).

Many of the effects of the thyroid on carbohydrate metabolism have no relationship with the pancreas. In hyperthyroidism the blood sugar curve is often high and prolonged after ingestion of glucose and almost invariably after lactose. During the period of absorption, the respiratory quotient is high. The fasting blood sugar in hyperthyroidism is normal, but there is a sharp rise after breakfast and often a slight glycosuria. Experimental hyperthyroidism causes a decrease of hepatic glycogen, also a diminution of cardiac glycogen. That of the muscle is more resistant. The glycogen is not changed in hypothyroidism or only slightly reduced except in advanced states of insufficiency or cachexia, when it decreases markedly. The glycogen mobilization is diminished during the

action of insulin or adrenalin. The acidosis inherent to hyperthyroidism may produce histological lesions in liver and heart. The sensitivity to insulin is augmented in hypothyroidism with slow recovery from hypoglycemia and danger of convulsions and death in shock. In hyperthyroidism, the sensitivity to insulin is generally lowered except for the stages of depletion of glycogen. Coexisting hyperthyroidism and diabetes aggravate each other mutually. The excess of thyroid hormone may have directly a damaging effect on the islands of Langerhans. Thyroid feeding has not produced diabetes in animals with intact pancreas. If the pancreas is reduced in size by operation or damaged with pituitary extract, thyroid feeding will cause diabetes with polyuria and acidosis. This effect, reversible at the beginning, becomes permanent with prolonged medication. The resulting diabetes is called metathyroid diabetes. While hyperthyroidism is not more frequent among diabetics than in the general population, the incidence of diabetes is markedly higher among hyperthyroid patients. In patients having both ailments simultaneously immediate and ample thyroidectomy is imperative. The diabetogenic action of the thyroid is weaker than that of the pituitary. Thyroidectomy does not improve the diabetes in pancreatectomized dogs. In human diabetics, total thyroidectomy causes a slight increase in carbohydrate tolerance and a reduction in insulin requirements. However, the myxedema thus produced is a disadvantage that far outweighs the slight improvement in the diabetic state.—A.E.M.

HURXTHAL, L. M.

Experiences with the use of desiccated thyroid. Methods of detecting self-induced hyperthyroidism, with a report of a case in which auricular fibrillation occurred. *N. Y. State J. M.* 44: 2217 (1945).

Heart pain in myxedema may occur at different times and under different circumstances. It may begin with the onset of myxedema and may be relieved as treatment progresses. On the other hand, it may increase with routine treatment and may occur even with small doses of thyroid in some patients. Anginal pain is unusual before treatment. Coronary infarction or prolonged anginal seizures may occur at onset of treatment, when dose is increased or when patient appears to be stabilized. In general, the younger the patient, and the shorter the duration of the disease, the less chance there is of the

development of angina pectoris. A young patient with angina before treatment is likely to obtain relief with treatment. The dose is reduced on appearance of sternal or precordial pain and continued at that level for one or two months. All thyroid should be discontinued for several weeks following anginal seizure or coronary infarction. In panhypopituitarism, secondary myxedema and pituitary hypoadrenalism may be present. In these cases, thyroid may be poorly tolerated and may precipitate an acute adrenal insufficiency. The use of desiccated thyroid when not specifically indicated has several dangers. Ordinary doses may not have a serious effect on the heart of a patient without myxedema unless coronary insufficiency is present. Larger doses may activate a latent diabetes. Exophthalmic goiter has been reported following the use of thyroid for weight reduction. Patients may take thyroid secretly for weight reduction or as a source of energy or mental stimulation. This possibility should be suspected in patients who have clinical evidences of hyperthyroidism with a normal thyroid gland on palpation. It should be considered in patients who have had a subtotal thyroidectomy and who continue to be thyrotoxic without recurrent or persistent hyperplastic remnants. The basal metabolic rate is high and iodine is found in large amounts in the urine and in the blood. With the exception of exophthalmos and an abnormal gland, induced hyperthyroidism is indistinguishable from the true hyperthyroidism and considerable detective work is sometimes necessary to establish thyroid addiction.—*M.B.G.*

PALMER, E. V.

Hyperthyroidism and thiouracil. *Ann. Int. Med.* 22: 325-364 (1945).

Fifty unselected cases of thyrotoxicosis have been treated with thiouracil at the University Hospital in Baltimore for varying periods up to ten months. In 42 of the cases the management has been exclusively medical. Thyroidectomy was performed in eight cases for cosmetic reasons or because the patient was unable to return weekly for laboratory studies. Thiouracil was administered in a dosage of 0.1 gm. every three hours for three days; 0.1 gm. every four hours for three to six days and then 0.4-0.5 gm. daily until sustained clinical improvement was observed. A maintenance dosage of 0.1-0.3 gm. daily was usually arrived at within three months. Adjunctive therapy in cases most

recently treated consists of sodium bicarbonate with each dose of thiouracil, cevitamic acid, liver extract, multi-vitamin concentrates either thyroxin or desiccated thyroid. Patients were hospitalized until the basal metabolic rate had undergone a sustained fall. No case failed to respond to thiouracil although some responded more satisfactorily than others. Cases receiving exclusively medical management have now been off thiouracil for three months and have so far experienced no recurrent thyrotoxic symptoms. Patients relapsing cause thiouracil was discontinued too soon because of intercurrent infection or emotional stress have responded as satisfactorily to a second course of thiouracil therapy as the first. In the author's opinion, the administration of thyroxin or desiccated thyroid did not improve the response to thiouracil and had the following advantageous features: (1) increase in subjective well-being; (2) prevention of pitting edema; (3) prevention of ocular irritation in patients with exophthalmos; (4) prevention of the enlargement of the gland produced by thiouracil therapy. Toxic reactions comprised: (1) 1 case of transient leukopenia; (2) three cases of microscopic hematuria and crystalluria; one case of classical pityriasis rosea, probably unrelated to thiouracil. The author suggests that the thiouracil effect is brought about by depression of normal enzyme reactions of the thyroid gland in general but especially the pituitary (leading to suppression of synthesis of thyrotrophic stimulating hormone) and of the thyroid itself (leading to inhibition of iodine uptake).—*J.M.*

SCHWARTZ, A. R.

Exophthalmic goiter in children. *Arch. P.* 62: 214 (1945).

The author reports the case of an infant aged two years and three months who developed classical signs of exophthalmic goiter including exophthalmos, nervousness and restlessness, failure to gain weight, excessive perspiration, flushing of skin, enlargement of the thyroid gland, tachycardia, and low serum cholesterol. Because of the child's age and the severity of the disease she was given x-radiation to the thyroid gland. This caused an improvement in her condition for seven months and then the manifestations recurred in an exaggerated form. At this time a bilateral thyroidectomy was performed, following which the patient had an acute exacerbation of the thyrotoxicosis and died one hour post-operatively. The rem-

and showed extremely marked papillary hyperplasia of the thyroid with lymphoid infiltration. A post-mortem was not performed. The author reviews the literature and points out that although this condition is extremely rare in children it does occur and therefore should be borne in mind.—*E.C.R., Jr.*

THOMPSON, W. O., AND P. K. THOMPSON

Changes in the treatment of toxic goiter produced by thiouracil. *J. Lab. & Clin. Med.* 30: 354 (1945).

The authors draw certain conclusions about the effectiveness of thiouracil in toxic goiter. In proper dosage, thiouracil lowers the basal metabolic rate, and maintains a lowered rate. After one or more months of treatment the drug may be omitted without the recurrence of symptoms. This suggests that it may afford a satisfactory treatment for the thyrotoxic state without recourse to other forms of therapy. The value of

the drug in preoperative preparation of patients has been proven.—*T.H.McG.*

## PARATHYROID

SEVRINGHAUS, E. L. AND RUTH ST. JOHN

Parathyroid tetany treated with massive doses of vitamin D. *Semana méd. Tomo Cin-cuentenario*, 1: 327 (1944).

Six women with severe and persisting hypoparathyroid tetany were maintained free from symptoms by oral medication with vitamin D and calcium salts. The treatment covered a period of two years or more. One patient went uneventfully through a pregnancy and delivery during that time. The vitamin D doses varied between 150,000 and 400,000 units daily. There were no signs of hypervitaminosis. The diet was not restricted as far as meat, eggs and milk were concerned.—*A.E.M.*





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## Further Observations on the Value of the Pregnandiol Test for Pregnancy<sup>1</sup>

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OBSERVATIONS on the excretion of pregnandiol in the urine of women, relative to corpus luteum activity and progesterone secretion, have led to the conclusion that the presence of pregnandiol in the urine during amenorrhea signifies a normal pregnancy (3, 10, 17). On this basis we presented in 1944 a simple, rapid method for the determination of pregnandiol in urine (color reaction) as a diagnostic test for pregnancy (9).

The present report summarizes data on 248 patients, of which 155 were tested since the previous report. The results indicate that the pregnandiol color reaction is at least as accurate a diagnostic test for pregnancy as is the Friedman test. Added experience has led to technical refinements which improve the reliability of the procedure.

### FURTHER OBSERVATIONS ON THE TECHNIQUE OF THE TEST

The technique for the pregnandiol determination has been detailed elsewhere (9). The entire procedure requires two and one half to three hours to complete. From four to six specimens can be conveniently tested simultaneously. The chemicals are inexpensive, and the equipment employed is standard in clinical laboratories. No animals are needed. The rapidity and economy of the determination are self-evident.

From further accumulated experience, it has been found practical to take several precautionary measures to insure against interference with the final color reaction, viz.:

1. New reagent solutions should be tested for their production of spurious colors. Each solution, in the volumes employed in the test, is evaporated to dryness in the hood. Ten cc. of conc.  $H_2SO_4$  is added to the cooled residue of each solution. Any solution giving a visible color reaction with the conc.

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$\text{H}_2\text{SO}_4$  must be discarded and be prepared anew or redistilled.

Commercial absolute alcohol has contributed to false color reactions. Preparation of absolute alcohol from commercial absolute alcohol by the method of Lund and Bjerrum (12) has eliminated the misleading color factor.

2. Preparation of 2 per cent NaOH in absolute methanol solution for use over a long period of time has led to "false negative" reactions. This solution is now prepared in the laboratory as follows:

- a) A solution of from four to eight per cent NaOH in methanol is prepared in a *dry* Erlenmeyer flask.

TABLE 1. SUMMARY OF RESULTS<sup>3</sup>

Clinical state	Pregnandiol test		Friedman test	
	Correct	Incorrect	Correct	Incorrect
Normal pregnancy	116	8	96	12
Amenorrhea (not pregnancy)	106	9	75	9
Corpus luteum cyst	0	1	1	0
Hydatid mole	3	0	0	3
Syncytioma	1	0	0	1
Testicular tumor	4	0	3	1
Total	230	18	175	26
Accuracy	92.7%		87.1%	

<sup>3</sup> All patients checked by clinical follow-up.

- b) The mixture is filtered through a *dry* sintered glass filter to remove the precipitated carbonate.
- c) The NaOH concentration of the filtrate is determined by titration with N/10  $\text{H}_2\text{SO}_4$ .
- d) The filtrate is then adjusted to a concentration of two per cent with absolute methanol.
- e) The solution is *freshly* prepared every two to three days.

3. Neglect in observing the final stages of the toluene or ethanol evaporation [steps B-7 and D-4 of the "Technique" (9)] may result in puzzling color reactions. Charring of the residues has led to dull, dirty, and light brown colors. These are easily distinguished from the true color reaction. The use of a fine stream of air to eliminate the last

traces of liquid from the vessel, which has been removed from the hot-plate, hastens evaporation and prevents charring.

Experience has led us to change the standard for a "positive" color reaction. Previously only an orange color was considered "positive." Quantitative studies using a spectrophotometer indicate that an orange color is equivalent to 1 mg. of pregnandiol per 100 cc. of urine,<sup>4</sup> or an excretion of approximately 15 to 20 mg. of pregnandiol per 24 hours. This range is higher than that reported in very early pregnancy (1) (2), and a standard based upon such an excretion would and did lead to false "negative" results. Therefore, the standard has been fixed at a color equivalent to a 24-hour pregnandiol excretion from 6 to 8 mg. The new minimum "positive" color is deep yellow.

#### RESULTS

The first morning urine specimens of women with amenorrhea, who presented obstetrical diagnostic problems, were examined by the pregnandiol color reaction and by the Friedman test. The urine of males who had testicular tumors was also similarly tested.

Table 1. summarizes the results obtained in 248 patients. Of these, 124 had normal pregnancies. Results were recorded as correct in 116 cases and incorrect in eight cases. "Positive" color reactions were obtained as early as five days after the first missed period, and more than 60 per cent of the patients were tested in the first four weeks after the missed period (see Table 2). Some of the patients in this group, prior to the pregnancy, exhibited abnormalities such as irregular menses, functional sterility, fibromyomata, and pulmonary tuberculosis.

The Friedman test was "positive" in 96 cases. Twelve errors were recorded, two occurring as late as the third month of pregnancy.

<sup>4</sup> In the procedure employed, Na pregnandiol glycurate is hydrolyzed. The color reaction is a measure of total pregnandiol excretion (free plus combined). Data pertaining to pregnandiol excretion (1, 2) represent metric determinations of Na pregnandiol glycurate which are expressed in terms of pregnandiol.

In the 115 patients with amenorrhea in whom suspected pregnancy was later ruled out, the pregnandiol color reaction was found correct in 106, and incorrect in 9. Table 3 lists the results obtained in this group according to clinical diagnosis.

Light "false positive" results were recorded in four groups of patients (two in each group). Among these groups were those with (1) delayed menses, (2) irregular menstrual cycles, (3) fibromyomata, and (4) early menopause. Four of these eight also showed "false positive" Friedman tests. A correct evaluation of the cause of these errors is not possible at present.

The occurrence of corpus luteum cysts has been suggested as a source of incorrect "positive" reactions. The presence of one such cyst in this series emphasizes its infrequent occurrence. The color reaction became negative two days after the surgical removal of the corpus luteum cyst.

The diagnosis of "ovarian cyst" was made in five additional patients, but pregnandiol was not present in the urine.

It has been demonstrated that the urines of patients with hydatid mole give strong

of a syncytioma—a tumor of the chorion. The color reaction prior to hysterectomy was "negative," the Friedman test "positive." It is believed that the syncytioma should be grouped with other chorionic neoplasms, such as the hydatid mole and chorionepithelioma.

Four patients with testicular tumor were encountered among the males, and these gave

TABLE 3 CLASSIFICATION OF THE NON PREGNANT AMENORRHEA GROUP

Clinical diagnosis	Pregnandiol test		Friedman test	
	Correct negative	Incorrect false positive	Correct negative	Incorrect false positive
Delayed menses	38	2	25	4
Menopause	11	2	8	0
Irregular menses	6	2	3	0
Fibromyomata	2	2	2	2
Ovarian cysts				
(a) Corpus luteum	0	1	1	0
(b) Parovarian	1	0	1	0
(c) Chocolate cysts	1	0	1	0
(d) Polycystic ovaries	1	0	1	0
(e) Unclassified	2	0	0	1
Hypothyroidism	4	0	3	1
Lactation	2	0	1	0
Tuberculosis	1	0	—	—
Pelvic inflammatory disease	2	0	1	0
No diagnosis	35	0	28	1
Total	106	9	75	9

TABLE 2 PATIENTS WITH NORMAL PREGNANCY GROUPED ACCORDING TO DURATION OF AMENORRHEA

Menses overdue	Pregnandiol test		Friedman test	
	Correct positive	Incorrect false negative	Correct positive	Incorrect false negative
1 week	15	0	13	3
2 weeks	28	2	24	4
3 weeks	12	1	12	0
4 weeks	14	4	14	3
More than 4 weeks	26	0	11	2
Not known	21	1	21	0
Total	116	8	95	12

positive Friedman reactions due to the excretion of large amounts of luteinizing hormone and contain small amounts of pregnandiol. The three patients tested in this series (Table 1) did not excrete sufficient pregnandiol to give a "positive" reaction. Histological examination of the uterus, removed from a woman in whom a hydatid mole was suspected, revealed the presence

uniformly "negative" pregnandiol reactions. A patient with a dysgerminoma in this group gave a "positive" Friedman test.

The use of the pregnandiol color reaction in the prognosis of threatening abortion [noted in our previous publication (9)] has been extended and will be reported at a later date.

#### DISCUSSION

The present report summarizes the experience to date in this laboratory with the pregnandiol color reaction as a diagnostic test for pregnancy. The results indicate that the color reaction is at least as accurate as the Friedman test.

The accuracy obtained in this laboratory with the Friedman test (87 per cent) is not as high as most investigators report. Davis and Walker (5), Friedman and Lapham (7), Magath and Randall (13), Reinhart and

Scott (14), Sondern and Silverman (16), Zisman (18), to list a few, recorded accuracies of 92 to 99 per cent. In a review of the literature, King (11) found variations in accuracy from 84 to 100 per cent. Davy and Sevringhaus (6) emphasize that early pregnancy and diagnostic problems relating to pregnancy should form the basis of analysis. With this in mind, they reported an error of 10 per cent in 425 patients tested by an immature rat method, the immature female rabbit and/or the Friedman technique.

The majority of the patients in the present series presented problems in diagnosis, and more than 60 per cent were tested in the four weeks after the onset of amenorrhea. It therefore becomes more understandable why the accuracy in this series with the Friedman test is lower than that usually reported.

The Smiths state (15), "...it is not sufficiently recognized by most practitioners that the pregnancy test—whatever method is used—is not infallible." This important practical dictum serves to emphasize the fact that a pregnancy test should be considered as an adjunct to clinical judgment in problems concerning the diagnosis of pregnancy. Physicians are inclined to be impressed by the stated accuracy of pregnancy tests and seem to forget that errors do occur (4).

In a thoughtful editorial review of pregnancy tests, Smith and Smith (15) state that "false negative" results would be expected with the pregnandiol color reaction, since "pregnandiol excretion in early pregnancy is frequently no higher than in the non-pregnant woman." It should be repeated and stressed that the pregnandiol color reaction as a diagnostic test for pregnancy is based on *the presence of pregnandiol in the urine of women who have missed at least one menstrual period*. The relative pregnandiol excretion, which the Smiths emphasize, is not the significant feature. From their objection one would expect "false positive" rather than "false negative" results to interfere with the accuracy of the color test.

By changing the minimum "positive" color to deep yellow as indicated above, the sensitivity of the test was increased and it

became possible to evaluate this divergence of thought. The number of "false positive" reactions was not increased by this change in standard. Several results which would have been interpreted as "negative" by the older criteria were thus correctly judged to be "positive."

It has been asked whether patients with irregular menses might not give "false positive" results due to delayed ovulation or prolonged corpus luteum activity. In this series, the urine of twelve women who had irregular cycles was tested. Four patients had become pregnant and gave correct "positive" color reactions. Six who were not pregnant showed no pregnandiol in the urine. Two patients gave "positive" reactions which were recorded as incorrect. From this small series and these incomplete data it is not possible to state whether delayed ovulation had occurred, whether corpus luteum activity was prolonged, or whether an early pregnancy with subsequent abortion had not been detected clinically.

Failure to observe the precautions in performing the test indicated above may lead to incorrect results. Technique is important in such a chemical procedure. Therefore, the directions outlined, including the precautionary measures, should be followed closely.

Technically the procedure is simple and does not involve laborious, constant effort (8). There are steps where the test may be interrupted (B-7, C-3, D-4). Since six tests can be performed simultaneously in three hours, the actual time devoted to each test is half an hour. In our hands this is less time than has been found necessary to devote to an individual Friedman test.

#### SUMMARY

Results of the pregnandiol color reaction test for pregnancy employed in 248 patients involving obstetrical diagnostic problems indicate an accuracy of 92 per cent. The accepted Friedman test was recorded as 75 per cent correct in this same series.

The advantages of the pregnandiol test are reemphasized in this report. Technical

ements and precautionary measures are used. The standard for a "positive" reaction has been altered to a deep yellow color which does "false negative" results and does not increase the incidence of "false positives." The infrequency of the occurrence of an corpus luteum cysts is indicated. It does not therefore affect the accuracy of pregnancy test. Patients with hydatidiform and chorionic neoplasms do not excrete sufficient pregnandiol to give a "positive" reaction.

It is stressed again that the basis of the test is the presence of pregnandiol in the urine of women who have missed at least one menstrual period.

# ACKNOWLEDGMENTS

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# Testosterone Propionate in Treatment of Senile Pruritus<sup>1</sup>

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IN RECENT years geriatrics has become an important part of medicine. Geriatrics may be defined as the study of the diseases of old age. Stieglitz (17) states that it is useful to consider that most of the clinical problems related to geriatrics start at about 40 years of age. The so-called degenerative disorders become more frequent at this period, and their menace is greatest in the years from 40 to 60. If health can be maintained during this critical time, the probability of long disability and uselessness because of chronic illness after the age of 60 will be greatly reduced. Bancroft (1) considers the age of 65 years as marking the beginning of the period of old age. According to Piersol (13) there are no diseases exclusively affecting the aged; there are certain changes which occur with such frequency in the aged that they can be considered as physiologic. These include graying of the hair; atrophy of the lymphoid tissues; the senile type of emphysema, with the resultant decrease in vital capacity; osteoporosis of the long bones and an increase in the size of the flat bones; arcus senilis; atrophy of the intervertebral discs, with resultant decrease in height; decrease in the papillary beds of the skin, causing a pallor which may be mistaken for anemia; general decrease in, or absence of, the deep tendon reflexes; and atrophy of the thyroid, liver, spleen, kidney, and all other organs except the heart.

The changes in the skin include an increase in pigmentation of the exposed parts, a decrease in water and fat content, and a decrease of elasticity and growth and regenerative capacity. The ability of wound tissues to heal is greatly retarded because of the decrease in the capacity for regeneration. Loss in elasticity seems to result from atrophy and degeneration of the elastic connective tissue fibers, and perhaps partly from the decrease in the subcutaneous fat. A decreased secretion of the sebaceous glands may be responsible for the dryness of the skin in the aged. According to Carlson (3) the causes of the changes in structure and function in the human body with age are still obscure. Some may be the result of the genetic constitution of the individual or species, and some may be about through the accidents of living, such as faulty diets, infections, over-work, laziness, and gluttony. Heredity probably plays a primary role; however within a species, heredity is a factor in the life span of the individual and also even of the various organs within the individual, irrespective of environment, habits or disease. Nevertheless, it is practically impossible to separate the factors of aging from the effects of impairment due to accidents or disease. Davis (5) believes that the involutional processes which lead to senescence may be influenced by all factors which in any way modify cellular metabolism.

Senile pruritus is a common variety of generalized pruritus which is seen in persons of advanced age, and is probably a result of the generative changes in the skin, with

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ted dryness and defective reparative powers. The diagnosis of senile pruritus must be differentiated from pruritus of the aged which has causes other than degenerative. The criteria for making a diagnosis of senile pruritus are not well founded. In our series cases we made our diagnosis by a process of elimination and by the presence of certain degenerative changes. A generalized pruritus can be produced by a variety of conditions; hence, the diagnosis of "senile pruritus" is to be made only after other causes have been excluded. We considered the exciting cause of senile pruritus the atrophy of the entire thickness of the skin, including its appendages. The atrophy causes a thin, dry, irritated skin, and leads to generalized itching, migratory, generalized pruritus, arteriosclerosis (arteriosclerotic changes can often be noticed in the retinal vessels long before they are noticeable elsewhere), arcus senilis, thick dry skin on exposed surfaces, and a definite loss of elasticity were among the criteria required for diagnosis. Patients that had some other disturbances which are known to cause a generalized pruritus were not included in our series. The Kahn test, blood counts, and urinalysis were normal in all cases reported. The following conditions were eliminated as possibly responsible for or contributory to the pruritus: asteatosis, allergy, use of drugs, functional disorders, skin infections, and skin infections such as scabies and pediculosis.

Goldman and others (7) believed that atrophy in some of the cases of senile pruritus was caused by local or constitutional changes incidental to a sex hormone deficiency. They obtained good results from testosterone therapy in 12 out of 16 cases; in our remaining cases were improved.

Senile atrophy accompanied by senile pruritus is seen frequently in our dermatology clinics at Grady Hospital (Emory University). This study was undertaken to evaluate the effectiveness of endocrine therapy, based on the concept that the aging process involves hormone deficiencies (Benjamin). All our cases were males. The preparations used were testosterone propionate and

methyl testosterone.<sup>2</sup> Testosterone propionate was given by injection and as an ointment, and tablets of methyl testosterone were given orally.

Hollander and Vogel (9) recently reviewed some of the pertinent literature on the value of testosterone in certain dermatoses and reported eight cases in which postclimacteric dermatoses in males was treated with testosterone propionate. They call attention to Reichert's (14) statement concerning the treatment of juvenile acne, senile pruritus, and senile eczema with endocrine preparations. The first report of the effects of androgen treatment was by Leipner (11). He reported five cases of dermatoses which improved by this treatment. The ineffectiveness of this therapy in 22 cases of acne vulgaris was reported by Molitch (12). The effect of androgenic substances upon pigmentation was studied by Hamilton and Hubert (8). Other dermatoses treated by testosterone were studied by Lafitte and Huret (10); and Edwards, Hamilton and Duntley (6). Riley (15) used testosterone propionate in 20 cases of acne vulgaris with irregular results. Promising results were noted by Cornbleet and Barnes (4) following intramuscular treatment of patients with acne vulgaris with testosterone propionate. Eight male patients having postclimacteric skin diseases were studied by Hollander and Vogel (9). They reported the effects of injections of testosterone propionate. Their results indicated amelioration of the symptoms. They concluded that in presenile and senile dermatoses this preparation is of definite value.

#### REPORT OF CASES

*Case 1, S.B.M.,* an American male of Irish descent, aged 63, a manager of a freight concern, was first seen August 2, 1943. He had enjoyed comparatively good health until January of 1943 when his wife died and he began drinking heavily (2 quarts of liquor a day). Since May he suffered from a generalized pruritus which has been treated by local applica-

<sup>2</sup> The drugs, supplied through the courtesy of Roche-Organon, were *Neo-hombreol*, a form of testosterone propionate (10 mg. supplied in 1 cc. ampules for S.C. injections) *Neo-hombreol* (M), a form of methyl testosterone, (10 mg. tablets for oral use), *Neo-hombreol*, a form of testosterone propionate, (M) (dosules, 4 mg., in an ointment base for local application).



tions of various antipruritic lotions with only temporary relief. In July he developed numerous boils. He was allowed only one pint of liquor daily by his physician. He was treated with large doses of vitamins by mouth and by injection. He also was given injections of stock vaccine, and the furunculosis gradually improved. Physical examination revealed several boils on the trunk. The skin of the entire body was dry and large plaques of erythema and scaling were present. Both extremities and the upper back were more severely involved and numerous excoriations on these areas could be seen. There was some follicular keratosis of the buttocks, outer thighs and upper arms suggestive of a vitamin A deficiency. The skin on the dorsum of both hands, on the neck and legs showed definite atrophy, loss of elasticity, and senile freckling. A few senile keratoses were present on the face. An early arcus senilis was present and early sclerosis of the retinal vessels was evident. Other physical and laboratory findings were normal. The prostate was normal. The patient continued to take vitamins by mouth, and in addition was given 100,000 units of vitamin A a day and crude liver extract intramuscularly three times a week. Locally oily, anti-pruritic lotions were used and fractional doses of roentgen rays were given at weekly intervals. The pruritus improved considerably after four weeks of treatment.

The patient did not return until January, 1944, at which time he had a severe recurrence of the pruritus, although the local and vitamin treatments were continued. At this time the liquor intake was decreased to one-half pint a day and he was also under the ministrations of a physiotherapist. He was given ultra-violet therapy twice a week and several stronger anti-pruritic lotions were used. Two fractional doses of roentgen rays were again given at weekly intervals but all treatment gave only temporary relief. On November 3, 1944 the pruritus was so severe that we decided to try testosterone, and 10 mg. were given by subcutaneous injection. This was repeated at intervals of five days for four doses. The pruritus had improved considerably at the end of this time, and the injections were continued at weekly intervals for five weeks. The pruritus became more severe after this ninth injection, and the testosterone was given every third day for three injections. At this time the patient was completely free of the itching and was given an ointment containing testosterone to rub on his skin once daily. The pruritus was controlled until February 3, 1945 when methyl testosterone tablets were prescribed. One tablet was taken daily by mouth. Within three weeks the pruritus began recurring, and two weekly injections of testosterone were given to bring it under control. Since then he has returned once every three to four weeks for an injection of testosterone. This seems to be sufficient to control the pruritus. The prostate has remained normal. However, a leukoplakia of the tongue was first noticed in January, 1945. Although he was advised against smoking, he did not stop until recently, and

the leukoplakia has increased in size. He smokes on the average more than one pack of cigarettes a day.

*Case 2, W.H.C.*, an American, male, aged 76, was first seen on January 4, 1945. Aggravated, migratory pruritus had been present for many years. During the past year the pruritus had progressively worsened. Roentgen ray treatment gave some temporary relief. Starch baths, sedatives, and local applications of various antipruritic salts gave a temporary relief for a few hours each day. His health had always been good. Except for a prostatectomy, he had had no serious illness. Most of his life was spent outdoors with plenty of exposure to sun. He drank liquor only occasionally, and smoked moderately. The skin on the entire body was visibly thin, and atrophic, with considerable loss of elasticity. Senile freckling was present on the dorsum of the hands and on the face. A small squamous cell epithelioma, on the left ear, was removed. Arteriosclerosis was well advanced but he was mentally preserved. An arcus senilis was present. Numerous excoriations were present, especially about the neck and arms. Other physical findings were essentially normal. He had benign prostatic hypertrophy. The laboratory findings of the blood and urine were normal. He was given 10 mg. of testosterone by injection at intervals of five days, and the pruritus improved immediately and practically cleared after the fourth injection. He was also given a testosterone ointment to rub on his skin once daily. After four weeks the pruritus began recurring slightly and the testosterone propionate was continued at intervals of from three to four weeks. Only an occasional attack of itching occurred during the interval of each injection. The patient is still under treatment.

*Case 3, D.O.J.*, a white, American, male, 81 years of age, was first seen October 31, 1942. The patient had pneumonia and malaria in the past without ill effects. In 1937 he was seen by a dermatologist who made the diagnosis of neurodermatitis, and during the same year he developed a generalized erythroderma with exfoliation. His skin has remained dry and itchy ever since, and roentgen ray treatments and local medications have given him only moderate and temporary relief.

Physical examination showed a well developed elderly male, mentally alert and physically fit for his age. The skin appeared very dry and atrophic. There was a definite loss of elasticity and atrophy of the skin on the neck, anterior chest, dorsum of both hands, forearms and legs. Numerous excoriations scattered on the trunk and extremities were present. A well advanced arteriosclerosis was present. Arcus senilis were present. There was some atrophy of the anterior scrotum. The prostate was normal. Other physical and laboratory findings were essentially normal. Testosterone was given by injection at intervals of five days, and control of the pruritus was noticed after the eighth injection. Testosterone injections were given at intervals of ten days.

hen four were given at intervals of four weeks. The patient was then given the hormonal ointment to rub into his skin for a period of one month. The pruritus was so much improved that the patient discontinued treatment from April until October 20, 1944, when he returned with a recurrence of his pruritus. Testosterone was again given at intervals of five days for six doses. The dose chosen at this time was 25 mg. The pruritus improved immediately after the first injection. A few days after the second injection the patient was completely relieved. Three more injections were given, although no symptoms were present. He was again given the hormonal ointment to rub into the skin daily. The patient has not returned since December, 1944.

*Case 4, W M B*, a white, male merchant, 80 years of age, was first seen on October 18, 1943. He had several serious illnesses but has enjoyed good health for the past several years, except for a migratory generalized itching. The itching and stinging never involved the whole body at one time although all parts of the body have been involved. He has always scratched frequently but was advised against this about six weeks prior to our examination. The discontinuance of baths did not seem to help the pruritus which remained the same. Various local applications have been used with temporary relief. Exposure to sunshine, contact with wool, and the drinking of beer seem to aggravate the itching. The skin appeared dry, scaly and inelastic. Numerous excoriations were present. The skin over the anterior surfaces of the legs was eczematized. The skin on the dorsum of the hands, upper chest and on the sides of the neck was atrophic, scattered senile keratoses were present on these areas. There were numerous seborrheic keratoses on the back. Arteriosclerosis and arcus senilis were well advanced. There was a loss of deep tendon reflexes. He was not very alert mentally. He was constantly rubbing and scratching. A benign prostatic hypertrophy was present.

Testosterone was given subcutaneously at intervals of five days for ten doses before the pruritus was sufficiently controlled to give the patient noticeable relief. An ointment containing testosterone was prescribed to be rubbed in once daily. This was done for one month. There was no pruritus at the end of this time, but a complaint of stinging was still present. Methyl testosterone tablets were then prescribed in a dosage of 10 mg three times daily. After one month the patient returned with a recurrence of his pruritus, and the ointment again was prescribed. At this time a squamous cell epithelioma was removed from the left cheek. This malignant change appeared as a senile keratosis. He was again seen on May 15, 1944. The ointment of testosterone was still being used. At this time a squamous cell epithelioma was removed from the dorsum of the right hand. Because several senile keratoses present on the dorsum of the hands it was likely that the keratoses preceded the malignancy. The prostate was normal at this time. The pruritus was moderate and recurring.

There was still some stinging of the skin, sufficient to be annoying. The hormonal ointment was discontinued, and testosterone propionate again was given by injection at weekly intervals. Six weekly injections were given before the pruritus was again controlled. The subsequent injections were from three to six weeks apart, and seemed to be sufficient to control the itching. He would return whenever the itching would appear. One injection seemed to suffice for several weeks. This patient was lost from observation on November 13, 1944. At this time the prostate and general physical examination showed no change from our previous findings.

*Case 5, L W C*, a white, American, retired contractor, aged 72, was first seen on March 14, 1944. His chief complaint was a severe, generalized pruritus which has been getting progressively worse for three years. He has had various medical examinations but no reason for the pruritus was found. Local applications of various ointments and lotions would give him some temporary relief. His skin was dry, and scattered excoriations were present over the trunk and extremities. A scar was present on the left cheek where a skin cancer was removed several years previously. Numerous senile and seborrheic keratoses were present on the face. The skin on the face, neck, hands, and forearms showed definite atrophy and loss of elasticity. Arteriosclerosis was well pronounced, and the arcus senilis was very noticeable. The prostate was normal.

Testosterone was given by injection at five day intervals for five doses, without much relief. The injections were then given twice a week for five weeks, and, in addition, local injections of testosterone were used daily. The patient said he felt 50 per cent better at this time. The injections were continued at weekly intervals and the injections omitted. This was continued for five weeks. The condition remained about the same, and the injections were given at intervals of two weeks for three doses, and then at intervals of three weeks. The patient was given no treatment during July, and returned in August with a recurrence of his severe pruritus. Methyl testosterone was given three times daily by mouth, but after one month the pruritus and dryness of the skin were again as severe as on admission. On September 19th the patient again was started on testosterone by injection at five day intervals, and 20 mg doses were used instead of the customary 10 mg doses. The condition improved after six injections, but the patient became discouraged and discontinued his treatments.

*Case 6, C R G*, white, American male, age 68, was first seen on March 22, 1943. His chief complaint was a dry and itchy skin. The pruritus has been present off and on for ten years but has become severe during the past year. He has been diagnosed as having, and was treated for, seborrheic eczema and lichen planus. From March until August, 1942, he was given fractional doses of roentgen rays, crude liver extract by injection, stovarsol by mouth, and various anti-

pruritic emulsions, all without much benefit. His past health has been good except for the trouble with his skin.

When examined this patient was found to have an extremely dry and scaly skin. The back of the arms, hands and legs were erythematous, scaly and numerous excoriations were present. There was a definite loss of elasticity and senile freckling of the hands and face was present. Numerous senile keratoses were present on the face. Arteriosclerosis was well pronounced but the patient appeared mentally as well as physically alert. An arcus senilis was not very noticeable, and the prostate appeared normal. The laboratory findings were normal.

He was started on testosterone by injection at five day intervals. After seven injections he considered himself 60 or 70 per cent improved. The injections were continued until 20 injections had been given. The skin was clear at this time but moderate pruritus was still present; the patient believed himself more relieved than had ever been the case in the year in which the pruritus had become severe. Testosterone ointment was prescribed to be rubbed into the skin daily. After one month the patient called to report a recurrence of his pruritus. The injections were continued for two more weeks and in addition methyl testosterone tablets were given three times a day by mouth. Three weeks later, when he was seen at the office, the eruption and pruritus were almost as bad as when seen on his first visit. Further treatment was refused and the patient was not followed further.

*Case 7, B.D.*, white, American farmer, aged 67, was first seen on January 4, 1944. A severe, generalized pruritus had been present for the past two years. The patient had an operation for gall stones in 1930, but otherwise enjoyed good health. He appeared to be normal physically and mentally. An arcus senilis and arteriosclerosis were present, though they were not advanced. The skin was dry and scaly and showed considerable loss of elasticity and senile atrophy. Numerous seborrheic warts were present on the back, and several senile keratoses were present on the face. The prostate was normal.

Testosterone was given by injection every five days for a total of ten injections, with very little relief. Testosterone by mouth and daily inunctions of testosterone were added to the therapy. Ten more injections were given but the response was not marked and the patient became dissatisfied. Locally anti-pruritic emulsions were used but with only temporary relief.

*Case 8, B.M.*, a Turkish Jew, aged 72, was first seen in the dermatological clinic on January 4, 1944. His chief complaint at this time was a severe itching which was present for a period of 5 years and has been severe during the past several months. The pruritus would involve only parts of the body at any one time; however, all parts of the body have been involved at one time or another. He has been known

as a hypertensive for at least ten years. In 1934 he was diagnosed as having chronic cardiovascular disease with a blood pressure of 195/120. During the past two or three years he has had subacute pain brought on by exertion; relieved at first later by vasodilating drugs.

Physical examination showed the heart slightly increased in size. The rhythm was normal but the quality of sounds was poor, and a systolic murmur was heard over the precordium. There was a severe sclerosis of the blood vessels. His blood pressure was 150/90. There was a benign prostatic hypertrophy. A marked decrease of deep reflexes was present. Other findings were normal. The skin was dry, scaly and eczematized over the forearms and legs. There was loss of elasticity and some atrophy most pronounced on the dorsum of the hand and neck. Numerous scattered excoriations were present on the body and some secondary infection was present. Symptomatic treatment with calamine lotion and various anti-pruritics had been present for several months in the medical clinic but only temporary relief. It was decided to try testosterone propionate and a dose of 10 mg. was given at five day intervals for seven weeks. At this time the patient was considerably improved and the texture of the skin seemed more normal. The dryness was considerably less and the eczematization of the hands and legs almost disappeared. Two injections were given at intervals of two weeks, and two at intervals of three weeks. This seemed sufficient to control the pruritus. Methyl testosterone in doses of 10 mg. was given three times daily by mouth for six weeks at which time the patient reported that the pruritus had reappeared and was severe. An ointment of testosterone was prescribed and one dose was rubbed in daily for two weeks. The pruritus improved at this time and the treatment was continued for six more weeks. The relief was great, but not as much as when the injections were used. The treatment was discontinued during the summer months. The pruritus subsided but was not severe. On October 11, 1944 the pruritus became severe again. After four weekly injections of testosterone the itching improved considerably, and one injection every three weeks thereafter seemed sufficient to keep the patient comfortable. On January 7, 1945 this patient died of cardiac failure.

*Case 9, T.H.*, white American, aged 78, was first seen on February 10, 1943. This patient came to the hospital with an infected wound which was a result of "fighting" a few days previously. A generalized migratory pruritus was also a complaint at this time. The past history revealed meningitis and two attacks of pneumonia during childhood. Physical examination showed a man well preserved for his age. He was mentally and physically alert. His blood pressure was 155/85. There were no abnormal reflexes except for a slight decrease in the deep reflexes. The skin also was very dry and scaly and some atrophy and loss of elasticity was noticeable almost everywhere.

the body. An arcus senilis was present. Arteriosclerosis was present. He had an infected laceration of the right hand.

Symptomatic treatment was prescribed, giving temporary relief. The patient was seen periodically one year. The itching became progressively worse and in February, 1944, testosterone propionate was given at weekly intervals by injection. In six weeks the pruritus improved considerably, and the patient did not return until November 28, 1944. At this time the pruritus was severe again and he was given another injection. He would return at about monthly intervals for an injection. This would not control the pruritus completely, but sufficiently to keep him comfortable. Testosterone tablets were given to this patient but he refused to take them for one week, because they "did no good."

*Case 10, S B*, a white American, aged 70, was first seen by us on July 7, 1942. He gave a history of itching and a skin eruption since 1930. He had been diagnosed as having pellagra, and had been treated in the past with brewers' yeast and dilute hydrochloric acid. He was hospitalized, and a gastric analysis showed no free hydrochloric acid and a decrease in the total acid content. There was a mild secondary anemia. The differential leucocyte count showed a mild eosinophilia. Other laboratory findings were normal. The patient also complained of weakness and diarrhea. A generalized dermatitis over the legs and feet was present, and there was a noticeable lichenification on the dorsum of the feet. A similar eruption was present on both hands and forearms, with a lichenification of the dorsum of both hands. Desquamation consisting of large flakes was marked on the legs and forearms. A mottled brown pigmentation was present on the areas involved and also on the scrotum. The face showed a similar pigmentation and thickening of the skin. Although the dermatitis was not marked, some atrophy of the papillae was noted. A diagnosis of pellagra was made.

He was given liver extract by injection and 100 mg. of nicotinic acid by mouth. There was not much improvement after two weeks and the patient was discharged. He continued treatment at home, taking nicotinic acid and brewers' yeast. His condition improved some after several weeks of treatment. His diet was inadequate due to social and economic circumstances. This patient was seen periodically until January, 1943. At this time the dermatitis was very severe. The skin over the entire body appeared dry and scaly. Marked arteriosclerosis was present. We decided to give testosterone by injection at weekly intervals. After six injections of testosterone, which was given in addition to the brewers' yeast, a marked improvement in the skin was evident. The pruritus improved, although it did not subside. After ten weeks of treatment the dermatitis improved markedly and the patient felt better than he ever had since it was seen in 1942. The patient failed to return for a follow up.

# COMMENTS

It is our opinion that testosterone propionate is of definite value in the treatment of senile pruritus. Local applications of testosterone propionate are beneficial in some of these cases. In others no symptomatic improvement is obtained. Roentgen rays in subfractional and fractional doses may be used profitably, yet this treatment tends to aggravate the already dry skin. Recurrence of the pruritus limits the frequent use of roentgen therapy. In our series of cases oral methyl testosterone was found to be completely ineffectual. Methyl testosterone orally seems to be effective when the hormone is indicated and used in younger individuals, and this failure is not readily explained, although it may be due to a lower absorptive factor. Testosterone propionate by injection was fairly successful in controlling the pruritus. From an economic standpoint, it is more advantageous to the patients. The hormone when given subcutaneously yielded the best result. After the pruritus was under control the treatment intervals were increased. An effective interval for injection in our cases was from three to four weeks. The subcutaneous implantation of testosterone pellets as recommended by Feldman *et al* (7) will probably prove to be the treatment of choice in cases of senile pruritus which are resistant to symptomatic local treatment. Testosterone is contra-indicated in malignancy of the prostate. For this reason the prostate glands of all patients should be examined prior to and during the testosterone therapy.

The skin in some of our cases showed eczematization. Frequently the extensor surfaces of the forearms and legs and occasionally the face would have an appearance of a subacute dermatitis. In several cases these areas would show an early lichenification of the skin which apparently was caused by friction and rubbing of the areas involved. With an improvement of the pruritus the skin manifestations would also improve and eventually clear up. In some cases the erythema was pronounced and a localized edema was present. The first impression was that of a contact dermatitis. However, this dermati-

tis, as a rule, was resistant to local symptomatic treatment.

The dryness of the skin seemed to be less pronounced while the patients were under treatment. This clinical observation would support the findings of Rony and Zakon (16). In their report six prepubertal boys received testosterone propionate parenterally for two weeks. Biopsies from the pubic region made just before and two or three days after treatment showed decided increase in number and size of sebaceous glands in all subjects, which the authors consider direct evidence of a stimulating action of androgen on the sebaceous glands in man.

Several of our cases merit special comment:

*Case 1, S.B.M.* The condition was apparently senile pruritus in an alcoholic. The pruritus and dermatitis were controlled by testosterone when vitamins orally failed to improve the patient's skin condition. It was interesting to find that the dryness and accompanying dermatitis and eczematization improve along with the relief of the pruritus. There is apparent stimulation of the inactive sebaceous glands which function again under testosterone therapy.

*Case 3, D.O.J.* In the beginning, eight injections of testosterone were given subcutaneously in 10 mg. doses before the pruritus was sufficiently relieved. When the testosterone was discontinued the pruritus recurred. The testosterone was given in 25 mg. doses and the response was immediate. It seems likely that 10 mg. dosages of testosterone are rather small and larger doses should be given in order to give the patient early relief. In none of our cases did the testosterone therapy stimulate any sexual feelings at any time during the course of treatment.

*Case 10, S.B.* Although pellagra was present, the skin changes were not responsive to liver and nicotinic acid until testosterone was used. A combination of pellagra and senile pruritus apparently was present.

#### SUMMARY

Ten patients having senile pruritus, were treated by local applications and parenteral injections of testosterone propionate and by

oral methyl testosterone. Only those that had failed to respond after other prolonged symptomatic measures were chosen. Seven patients responded favorably; two improved; and one failed to show any alleviation of the condition. Testosterone propionate given by injection and by inunction was of great value. No improvement was obtained with oral methyl testosterone.

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# The Reliability of the Aschheim-Zondek Test in Pregnancy

A report of two thousand routine tests)

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THE PROCEDURE introduced by Aschheim and Zondek has proven to be very reliable for the detection of early pregnancy, as well as for the differentiation of pregnancy from hydatidiform moles and chorionepitheliomas. Many modifications have been introduced in the procedure, primarily in the quantity of urine, and the time and number of injections. These changes are immaterial, since the majority of publications now that regardless of the modifications, this test has proven to be highly accurate. The accuracy of the test has been repeatedly reported to be between 98 and 99 per cent.

Allen and Dickens (1930) (1) have emphasized the importance of performing the test on young mice. They state that the age of the mice should not exceed 24 days. These authors found that corpora lutea are usually found to be accompanied by corpora hemorrhagica. Corpora lutea were present without corpora hemorrhagica in only four of their 26 positive tests.

This report is an analysis of 2000 consecutive routine qualitative pregnancy tests performed on mice, at the Naval Medical School during a seven months' period (November, 1944, to June, 1945). Six hundred

and fourteen of these specimens were received by mail delivery from various areas of this country—from as far north as Connecticut to the southern area of Florida, and as far west as Oklahoma. The majority of these specimens were from two to four days in transit. Very few contained any preservative. The other 1386 specimens were received by messenger, the day procured.

## THE TECHNIQUE OF THE TEST AS USED AT THE NAVAL MEDICAL SCHOOL

The Endocrinology Laboratory requests that the clinician send either the first voided urine specimen, having a specific gravity of at least 1.015, or a specimen of serum.

All urine specimens received by mail are detoxified (shaking one part of urine with approximately three parts of ether) before being injected into the test animals. Four immature female mice, three to six weeks old, are routinely used for the test; however, during a period of scarcity of mice, three mice were used in 467 of these reported tests. The mice used for this study were not carefully bred or selected. The majority of these animals were obtained from four commercial breeders.

Each mouse is injected subcutaneously under the loose skin of the back, once daily for three successive days, with 0.25 cc. of urine or serum. On the morning of the fifth

<sup>1</sup>Received for publication Sept. 13, 1945.

<sup>2</sup>The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

day (approximately 90 to 96 hours after the initial injection), the mice are asphyxiated with illuminating gas, then secured with pins to large animal boards and opened. The number of corpora hemorrhagica and corpora lutea are counted on each ovary of all mice. The test is reported positive if one or more hemorrhagic follicles, or a definite corpus luteum is present on any one of the animals in the set. If the presence of a follicle is questionable the test is reported as doubtful and another specimen is requested. In the absence of both corpora hemorrhagica and corpora lutea, the test is reported as negative. The clinician is requested to forward his final conclusions on each patient, in order that the laboratory can determine the accuracy of the tests.<sup>2</sup>

### RESULTS

In this series, 118 of the tests were performed on serum and 1882 on urine. The results reported to the clinician are listed in Table 1. Positive tests were obtained on

TABLE 1. RESULTS OF TWO THOUSAND ASCHHEIM-ZONDEK TESTS

Type of specimen	Results obtained			Total
	Positive	Doubtful	Negative	
Urine	1310	83	489	1882
Serum	88	4	26	118
Total	1398	87	515	2000

approximately 75 per cent of the serum specimens and approximately 70 per cent of the urine specimens.

The accuracy of the Aschheim-Zondek test is demonstrated in Table 2. Only 844 of the 2000 reports were returned to the laboratory

TABLE 2. ACCURACY OF THE ASCHHEIM-ZONDEK TEST (Results of eight hundred and nineteen cases)

Results of test	Confirmed by clinical evidence	Very early pregnancies	Errors	Total tests
Positive	625		4	629
Negative	169	16	5	190

<sup>2</sup> The Endocrinology Laboratory of the Naval Medical

with final clinical conclusions. Four of 629 reported positive specimens were from non-pregnant women; whereas five of the reported negative specimens were from pregnant women. These five patients did not have early pregnancies and positive results should have been obtained. Therefore, these false negative reports are considered as errors. Sixteen of the negative reports were on specimens obtained from women in early pregnancy; two were specimens taken six days after the first missed menstrual period.

### POSITIVE TESTS ON NON-PREGNANT PATIENTS (FALSE POSITIVE REPORTS)

*Case #1:* The urine specimen was received by mail delivery. The test was negative. Before this test was completed, a second specimen dated three days later than the first specimen was received and the second test was positive. The final report states that the patient menstruates regularly and no clinical basis for pregnancy was found.

*Case #2:* This urine was received by messenger on November 30th. The test was positive. The clinician did not believe the patient to be pregnant, and the test was repeated and again found to be positive on a second specimen, December 6th. A third test on urine, December 14th, was negative. The test on serum on December 20th was also negative. This patient was not pregnant.

*Case #3:* The test on this urine was reported as positive. The clinician later reported that there was no evidence of pregnancy.

*Case #4:* This test on urine was reported positive. Repeated clinical examination showed no evidence of pregnancy.

### NEGATIVE TESTS ON PREGNANT PATIENTS (FALSE NEGATIVE REPORTS)

*Case #1:* This test was reported negative. Seven days later a repeated test was positive. All signs of pregnancy were present. An x-ray showed a fetus of approximately five months development.

*Case #2:* The first test was doubtful. A repeated test 14 days later was negative. A third test 41 days after the first test was

gative. An x-ray taken one month after the third test showed a fetus of approximately three weeks. All clinical signs of pregnancy were present.

*Case #3:* A urine specimen from a patient suspected of having an ectopic pregnancy gave a negative test.

*Case #4:* Two tests with a ten day interval intervening were negative. The second test is performed on a catheterized specimen. The clinician reported the presence of the fetal heart beat.

*Case #5:* A test reported as doubtful was repeated and reported as negative. A repeated clinical examination proved this patient was pregnant.

#### PATIENTS WITH EARLY PREGNANCY

Sixteen patients, of whom nine did not state the date of the last menstrual period, gave negative results in the first test and positive results on repeated tests. The clinical

TABLE 3 REPEATED TESTS, CASES OF EARLY PREGNANCY

Days after last menstrual period		
First test		Repeated tests positive
Negative	Doubtful	
34	35	45
35		46
37		47
38		50
40		53
41	47	54
		54
		55

ns reported these nine patients as having early pregnancies. (Both tests on one of these nine patients were made on serum.) The quantity of hormone present in the first specimen from each of these 16 patients apparently was insufficient to obtain positive results.

Table 3 demonstrates that there is a variation in the quantity of the hormone excreted. In some individuals the quantity of hormone present is sufficient to produce a positive test earlier in pregnancy than in others. Kurzrok (1932) (2) obtained a positive test one day after the missed period. One of the patients

in this series gave a positive test three days after the first missed menstrual period.

TABLE 4. PERCENTAGE OF MICE REACTING TO THE HORMONE<sup>3</sup>  
(When four mice were autopsied)

Number of tests performed	Number of mice	
	Reacting	Not reacting
303 tests	4 mice (100%)	All mice reacted
306	3 (75%)	1 mouse (25%)
95	2 (50%)	2 mice (50%)
96	1 mouse (25%)	3 (75%)
When three mice were autopsied		
187	3 mice (100%)	All mice reacted
176	2 (68%)	1 mouse (33%)
81	1 mouse (33%)	2 mice (68%)

<sup>3</sup> This includes tests on serum and urine.

#### PERCENTAGE OF MICE REACTING TO THE HORMONE

It well known that some mice will not react satisfactorily to the hormone present in the urine or serum. In 1344 positive tests, when at least three mice were still living on the morning of the fifth day, 1322 (26.8%) of the 4932 mice did not react; that is, no corpus luteum or hemorrhagic follicle was present on either ovary (Table 4).

#### COMPARISON OF REACTIONS IN MICE

Positive reactions were recorded as one, two, three and four plus; depending on the number of follicles and the number of ovaries reacting. Analysis of the results show that approximately 70 per cent of the positive specimens produced moderate reactions. Only five to seven per cent produced very marked

TABLE 5 COMPARISON OF THE INTENSITY OF REACTIONS IN MICE

Type specimen	Intensity of reaction			
	4 plus	3 plus	2 plus	1 plus
Urine	69 tests	235 tests	450 tests	556 tests
Serum	6	18	24	40
Total	75	253	474	596

reactions. There was no marked difference in degree of reaction between urine and serum (Table 5).



TABLE 6. COMPARISON OF REACTION TO AGE OF MICE  
(Showing results obtained in testing 664 positive specimens)

	Approximate age of mice in days <sup>1</sup>						
	21	24	28	30	32	35	42
Number of mice in age groups	54	134	278	325	372	513	773
Number of negative mice	24	32	65	74	86	141	124
Per cent of negative mice	44	24	23	23	23	27	33
Total corpora hemorrhagica	73	317	676	824	973	1290	862
Average hemorrhagic follicles per mouse	2.42	3.14	3.17	3.28	3.40	3.47	3.3
Total corpora lutea	235	800	1865	2486	3447	5531	3699
Average corpora lutea per mouse	7.83	7.93	8.75	9.90	12.05	14.89	14

<sup>1</sup> At time of initial injection.

## COMPARISON OF AGE OF MICE

As previously stated in this report, the statement has been published that the age of the mice should not exceed 24 days. Therefore, in 1000 tests the approximate age of the mice was determined and recorded. (Due to a scarcity of mice, all available immature female mice were used.) Only results obtained on mice injected with positive specimens were used in the computation of Table 6. These results show that a very high percentage of the young mice (21 day old group) did not react. The lowest percentage of negative reactions occurred in mice in the 28, 30 and 32 day old groups. The average number of hemorrhagic follicles and corpora lutea increased with the age of the animal.

SPECIFIC GRAVITY IN RELATIONSHIP  
TO REACTION

There appears to be no marked relationship to the specific gravity of the urine specimen and the degree of reaction (Table 7).

In this series of 1401 doubtful and positive urine specimens, the lowest specific gravity recorded was 1.003 and the highest was 1.040. There were five specimens with a specific

gravity less than 1.007, on which positive results were obtained. The majority of specimens (80 to 83 per cent) of each group had a specific gravity between 1.015 and 1.030.

## THE STABILITY OF THE HORMONE

As previously stated, some of the specimens were received by mail delivery two to six days after voiding. Very few of the specimens contained any preservative. Since the results of these tests appeared satisfactory, there is no reason to believe that the hormone deteriorated in transit. To further check the stability of the hormone, three specimens of urine giving a three plus reaction were divided into two portions. One portion of each specimen was stored in a refrigerator at (8 to 10° C.), and the other portion was kept at room temperature (20 to 30° C.). After 18 days of storage, all specimens were retested. The specimens stored at room temperature deteriorated much more than those stored in the refrigerator (Table 8).

## MORTALITY OF MICE DURING THE TEST

Various investigators have reported a high mortality in the mice used for pregnancy

TABLE 7. COMPARISON OF SPECIFIC GRAVITY TO DEGREE OF REACTION

Specific gravity of specimen	Degree of reaction				
	Doubtful	1 plus	2 plus	3 plus	4 plus
Number of specimen less than 1.015	8	34	23	22	3
Between 1.015-1.030	71	461	373	186	11
Between 1.031-1.035	7	56	49	24	1
Over 1.035	1	6	9	3	0
Total number of specimens in group	87	557	454	235	15
Average specific gravity of group	1.0222	1.0234	1.0236	1.0234	1.022

ests Ehrhardt (3) stated in 1931 that the mortality may be as high as 20 per cent

In this study, all urine specimens received by mail delivery were detoxified before being injected into the mice. The mice of each set were kept in glass jars, covered with perforated metal tops. In this series of 2000 tests, 360 mice were used, of which 135 died after the first injection (1 834%). During the last

TABLE 8 STABILITY OF THE HORMONE  
(Storage at room and refrigerator temperature)

Specimen	Original test	After 18 days storage	
		Refrigerator (8-10° C)	Room temperature
#1	3 plus	3 plus	1 plus
#2	3 plus	2 plus	1 plus
#3	3 plus	1 plus	negative

week of July and the first part of August 686 mice were injected with routine specimens, of which 13 died (1 89%)

The following procedure is used at the Naval Medical School for detoxification of urine specimens

(1) If the specimen is alkaline, it is acidified with 10% acetic acid (avoiding excess acid)

(2) Approximately 90 cc of ether is added to approximately 30 cc of urine in a separatory funnel. This mixture is shaken for about five minutes

(3) The two fluids are allowed to separate, by standing two or three minutes. The bottom layer of urine is carefully drawn off into a wide shallow dish. Following a small quantity of urine to remain in the separatory funnel. The remaining traces of ether are removed by evaporation, with the aid of an electric fan

(4) Approximately 1 gm of glucose is added to the detoxified specimen

#### SUMMARY

(1) The Aschheim Zondek Test is unquestionably a very reliable test for the detection of pregnancy. There were four errors (0 6%) in 629 specimens from pregnant women.

There were five errors in 174 specimens from non pregnant women

(2) Some women may excrete a sufficient quantity of hormone to give a positive test very early in pregnancy. In this study a positive test was obtained on a urine three days after the missed menstrual period. In seven instances, when the first specimen was tested less than two weeks after the missed period, the tests were negative. Repeated tests were positive

(3) Approximately 25 per cent of immature mice will not react to the hormone

(4) Mice react equally as well to serum as they do to urine from pregnant women

(5) The ideal age of mice for pregnancy tests was found to be between 25 and 32 days. A greater percentage of mice in this age group will react to a positive specimen. However, more hemorrhagic follicles and corpora lutea are found in older mice

(6) The mortality of mice in this investigation was less than two per cent

#### ACKNOWLEDGMENTS

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# Thiouracil Derivatives of Greater Activity for the Treatment of Hyperthyroidism<sup>1</sup>

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A CONTINUED investigation of compounds which inhibit the function of the thyroid gland has revealed that appropriate substituents on the thiouracil molecule confer a greatly increased activity. The compounds 6-ethylthiouracil and 6-*n*-propylthiouracil are among a group which are approximately ten times as active as thiouracil when tested in rats; compounds of this class have exhibited an activity far superior to any of some 300 thus far explored (2). Tests in rats have also shown that these derivatives exert a more lasting effect following a single dose than does thiouracil, a substance known to be rapidly eliminated from the body. These derivatives have the further therapeutic advantage of a greater activity-toxicity ratio; while they are more toxic than thiouracil on a weight basis they are considerably less toxic in acute and in chronic experiments when administered in quantities calculated on the basis of equivalent

anti-thyroid effect. A selected group of the more effective anti-thyroid compounds when tested in chicks likewise showed that these thiouracils were much more active than any other compounds hitherto investigated (6).

In view of these considerations it seemed fitting to test the effectiveness of ethylthiouracil and propylthiouracil in human beings suffering from hyperthyroidism. The small doses which have proved to be effective and the favorable results which have been observed show that these compounds are well suited to clinical use.

## OBSERVATIONS

The first clinical tests were made with ethylthiouracil. It was administered to fourteen patients in doses of from 20 to 100 mg. daily with the aim of determining the minimal dosage which would be uniformly effective. This limited trial revealed a high order of activity, but observations on this compound were not extended further for two reasons: it proved to be a difficult substance to synthesize, and animal tests subsequently revealed the propyl derivative to be somewhat superior both as to its antithyroid potency and as to its more prolonged action following a single dose. Subsequent observations were therefore confined to propylthiouracil administered in the form of tablets containing 25 mg. each, given by mouth at intervals of 8, 12 or 24 hours.

The pertinent clinical data on these

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<sup>1</sup> The thiouracil derivatives recently synthesized by Roblin and coworkers [Anderson, G. W., Halverstadt, I. F., Miller, W. H., and Roblin, R. O. Jr., *Studies on chemotherapy. X Antithyroid compounds. 5- and 6-substituted 2-thiouracils*, *J. Am. Chem. Soc.* (in press)], were made available for testing by Dr. Roblin and his associates of the American Cyanamid Company, Stamford, Conn. Tablets of 6-*n*-propylthiouracil were supplied by Dr. S. W. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.

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Compounds are summarized in Table 1. The 14 patients treated with ethylthiouracil received the compound for periods of from one to seven months; subsequently the treatment of eight of these patients was continued with the propyl derivative. In 29 instances propylthiouracil alone was used, and thus its effectiveness was observed in a total of 37 cases. For a period of two weeks one patient received isopropylthiouracil, a compound very similar in its properties to the ethyl derivative.

Most of the patients were unquestionable examples of Graves' disease; this diagnosis remained unestablished in Cases 1, 3, 6, and 7. The diagnosis of hyperthyroidism with nodular or adenomatous goiter was made in Case 15. One or more thyroidectomies had previously been sustained by Patients 3, 1, 26, 27, 31, 39, and 42.

The methods of study and general management of the patients were similar to that used in former studies on thiouracil and thiobarbital (3, 4). Eleven patients were under observation in the hospital when treatment was instituted; the others were ambulatory throughout. The only supplementary vitamins given were those which were prescribed during hospitalization as a part of hospital routine. The various accessory food factors which have been claimed to influence drug toxicities were purposely avoided in order not to complicate the comparison between these and earlier compounds.

Iodine therapy had been recently discontinued in 13 instances, and failure to respond promptly was attributed to this factor in Patients 9, 10, 20, 24, 32 and 39; in Patients 26 and 27 there was no delay in response.

The recovery of the patients so treated suffering from hyperthyroidism was similar in every regard to the familiar response to thiouracil. There were no significant variations in the relative rates of improvement of the several symptoms, signs, and laboratory evidences of the disease from the pattern commonly observed with thiouracil. It is notable, however, that there was no instance of any of the serious reactions which some-

times complicate thiouracil therapy.

The potency of these two antithyroid compounds is well illustrated by the rate of recovery following their administration in small doses. For example, 50 mg. daily of ethylthiouracil in Case 5 brought about symptomatic improvement in four days; in ten days reversion to normal rhythm of the associated auricular fibrillation occurred. The symptomatic recovery in Case 14 was equally rapid with 75 mg. daily. Propylthiouracil in a dose of 25 mg. once daily brought about a prompt relief of symptoms in Case 22; the basal metabolic rate fell from +43 per cent to +18 per cent, and the body weight increased from 40.9 to 47.3 kgm. (90 to 104 pounds) in 18 days. A weight gain of 8.6 kgm. (19 pounds) occurred in Patient 29 during the first 24 days of treatment with 50 mg. of propylthiouracil daily. Further convincing evidence of the antithyroid effectiveness of both substances was provided by the complete recovery of five of the six cases of thyrotoxic heart disease. Patient 9 had previously received iodine and had not responded satisfactorily before the treatment was changed to thiouracil. The other five patients experienced a complete restoration of normal cardiac function.

#### DOSAGE

One of the most difficult features in this type of investigation is the determination of the minimal dose of a compound for initial therapy which will be adequate in all cases to induce a prompt response. One manifestation of this difficulty is to be observed in the many publications on the use of thiouracil wherein one observes that scant attention has been given to the matter; as a consequence very little new information concerning the optimal dose of thiouracil which should be used during the early weeks of treatment has come to light. During the clinical trials with thiobarbital nearly a year passed before it was suspected that the dosages being used were excessive. This error was fostered by too strict a comparison between the experimental animal and man, thiobarbital had proved to be approximately

TABLE 1

Patient no.	Age & sex	Initial body weight (kgm.)	Dosage mg. (days) <sup>2</sup>	Additional diagnoses <sup>3</sup> and previous treatment	Response
<i>o-Ethylthiouracil</i>					
1	35F	82.0	75(33)100(1-f)50(1-f) 20(35)40(49)0(28) 100(42)	Anxiety state; ? hyperthyroidism.	BMR fell; anxiety state changed.
2	61F	56.8	50(30)0(281+)	Initial response to thiobarbital good. (Ref. 4, Case 12.)	Response continued; remained 11 mos. without treatment.
3	50F	54.0	50(20)30(42)50(49) 100(110)	Thyroidectomy 1925; rheumatic heart disease with failure; ? hyperthyroidism.	BMR fell; goiter developed; failure not improved.
4	28F	50.4	50(5-f)20(5-f)50(112)	Partial response to thiobarbital. (Ref. 4, Case 9.)	Continued response.
5	60F	46.8	50(5)0(2)20(30)30(21) 50(49)75(56)	Previous toxic reactions to thiobarbital and sulfadiazine. (Ref. 4, Case 4.)	Auricular fibrillation reverted 10 days.
6	54F	49.5	30(19)60(3)30(8)60(47)	? Hyperthyroidism.	BMR fell with 60 mg.; no systematic improvement.
7	30F	59.0	30(14)0(4)50(119)0(5)		None to 30 mg.; prompt response to 50 mg.
8	38F	73.1	60(18)0(4)75(119)	Thyrotoxic heart disease.	Slow response until dosage increased.
9	62M	82.7	75(71) [Thiouracil 400(160+)]	Iodine; thyrotoxic heart disease.	Delayed effect; responded to thiouracil; heart improved.
10	55M	53.1	75(20) [Thiouracil 300(47)]50(60)	Iodine; thyrotoxic heart disease.	No response in 20 days; good control after thiouracil; heart normal.
11	68F	44.0	100(42)0(2)100(1)	Thyroidectomy 1941.	Good response; urticaria; controlled by 0.4 gm. thiouracil.
12	35F	54.5	100(60)	Anxiety state; cirrhosis of the liver.	No effect (Not thyrotoxic)
13	35F	48.1	100(32)	Pregnancy.	Satisfactory response.
14	52F	50.0	75(60)0(10)	Thiouracil 11 mo. Remission, 4 mo.; iodine 5 mo. (Ref. 3, Case 8.)	Symptoms controlled in 4 days.
<i>6-n-Propylthiouracil</i>					
1	—	—	50(45)25(125+)	Ethylthiouracil.	Goiter developed with 50 mg. daily.
4	—	—	25(28)0(154+)	Ethylthiouracil.	Sustained remission, 5 mo. with treatment.
5	—	—	50(43)0(4)25(102)0(30)	Ethylthiouracil.	25 mg. daily adequate for remission.
7	—	—	50(116)0(60+)	Ethylthiouracil.	Remained well with 50 mg. sustained remission.
8	—	—	50(122)0(60+)	Ethylthiouracil.	Well maintained; complete remission.
10	—	—	50(152+)	Ethylthiouracil.	Early myxedema with 50 mg. daily.
13	—	—	50(131)25(54)	Ethylthiouracil.	Well controlled; pregnancy complicated.
14	—	—	75(122+)	Ethylthiouracil.	Well controlled.
15	51M	60.0	50(14)	Toxic adenoma.	When treatment was continued; adenoma removed.
16	37F	47.7	50(25)75(49)50(103)0	Thyrotoxic heart disease.	Prompt; all cardiac manifestations disappeared.
17	64F	48.1	50(184+)		Prompt fall in BMR.
18	49F	63.6	75(7)50(140+)	Thyrotoxic heart disease.	Symptoms controlled in 6 days.
19	41F	53.1	75(50)150(63)75(43+)		Somewhat delayed; 75 mg. possibly inadequate.
20	60F	47.7	75(32)150(63)75(36+)	Iodine 3 wks.	Delayed response.
21	48F	50.0	75(14)	Thiouracil several times; febrile reaction.	Marked effect in two weeks; thyroidectomy.
22	45F	40.9	25(153+)	Fever and leukopenia from thiouracil and thiobarbital. (Ref. 4, Case 13.)	Completely controlled by 25 mg. daily.
23	39M	63.6	75(118+)		Prompt.
24	27F	54.5	75(53)0(14)75(50+)	Iodine.	Delayed; recurrence with continued; second response.

TABLE 1—Continued

Patient no.	Age & sex	Initial body weight (kgm.)	Dosage mg. (days) <sup>2</sup>	Additional diagnoses <sup>3</sup> and previous treatment	Response
<i>Propylthiouracil—Continued</i>					
15	55M	56.3	75( <i>80</i> )150(7)75(20+)	Iodine; thyrotoxic myopathy; auricular fibrillation.	Moderately rapid; normal cardiac rhythm in 3 wk.; complete response delayed.
16	35M	78.1	50(114+)	Thyroidectomy 1943; febrile reaction to sulfadiazine and thiouracil. (Ref. 1.)	Prompt—no evidence of toxicity.
17	54F	65.4	75(14)50(104+)	Thyroidectomy 1928; iodine 2 weeks.	Prompt despite previous iodine.
18	56F	52.2	50(93+)	Rheumatic heart disease.	Marked improvement in 4 weeks.
19	50F	67.2	50(91+)	Good response to thiouracil; remission 18 mo. without treatment. (Ref. 3, Case 5.)	Prompt—8.6 kgm. weight gain in first 24 days.
20	53F	44.0	75(14)50(75+)		Immediate improvement; further recovery slow with 50 mg.
21	48F	82.0	50(46)75(36)50	Thyroidectomy 1943; severe exophthalmos.	Hyperthyroidism controlled; eyes unimproved.
22	53M	79.5	75(74+)	Heart failure; iodine 1 year.	Delayed.
23	60M	65.4	75(62+)	Peripheral vascular disease of legs; ophthalmoplegia; iodine 18 mo.; none 5 wk.	Prompt control of hyperthyroidism; eyes unchanged.
24	27F	49.5	75(65+)	Pregnancy; iodine 3 mo.	Slightly delayed.
25	45F	49.5	75(51+)	Two thyroidectomies.	Prompt.
26	26F	56.3	75(61)50	Pregnancy.	Rapid.
27	37F	52.2	75(52+)	Anxiety neurosis.	
28	45M	61.8	75(46+)	Anxiety neurosis; iodine 10 days.	Response began third week.
29	39F	52.7	75(26+)	Thyroidectomy 1939; iodine 15 mo.	Moderately delayed.
30	76F	41.8	75(28+)	Iodine several years; x-Ray treatment 1942.	Delayed.
31	44F	82.7	75(26+)		
32	44F	61.8	75(24+)	Thyroidectomy	Prompt.
33	49F	55.4	75(22+)		Moderately rapid.

<sup>1</sup> The dosages are expressed in mg. per day and the italicized figures in parentheses signify the number of days that the drug was administered.

<sup>2</sup> The diagnosis in all cases was uncomplicated hyperthyroidism unless otherwise indicated.

times as active as thiouracil in the rat (5) whereas it later was clear that it is free or four times as active as thiouracil in man (4). In the cases of ethyl- and propylthiouracil the animal tests showed a potency about tenfold that of thiouracil and if this ratio were to hold for man the initial dose could be about 40 mg. per day.

The data shown in Table 1 indicate that this estimate is a little too low. During the earlier trials the dosage of ethylthiouracil was changed frequently in order to establish a rough estimate of the required dosage. While some of the cases proved unsatisfactory for this purpose a fairly good approximation could be made. For example 50 mg. was adequate in Patients 4 and 5 while 20 mg. was not. Patient 7 continued to lose weight

and to show a rising basal metabolic rate with 30 mg. daily but recovered rapidly when the dose was increased to 50 mg. Patient 8 responded definitely to 60 mg. daily but the rate of improvement was slow until the dosage was increased to 75 mg. daily. These limited data indicate that the initial dose of ethylthiouracil should be about 75 mg. daily.

In view of these considerations propylthiouracil was usually given in a dose of 75 mg. daily. In several instances the rate of the response seemed unduly slow, and for this reason Patients 19, 20 and 25 received 150 mg. daily for a short period of time and this larger dose seemed to accelerate the rate of recovery in one instance (Patient 20). It is debatable whether the larger dose was

of thiouracil and thiobarbital under similar experimental conditions indicates that these derivatives represent an improvement over the parent compound. This conclusion is reinforced by the observation that patients tolerated ethyl- and propylthiouracil well although showing sensitivity to thiobarbital or to thiouracil itself. The satisfactory response induced by these drugs in such small doses and with such a low incidence of toxic reactions appears to justify their further trial.

It has been pointed out that an estimation of the minimal dose of an antithyroid compound which will be uniformly effective in the control of hyperthyroidism is most difficult. The two variables contributing to this difficulty are the individual differences in dosage requirement and the wide variation in the rate of response. Consequently it is not possible to state with accuracy the relative antithyroid activity of these new derivatives as compared with thiouracil. It has been the general impression that the initial dosage most commonly used *i.e.* 50 or 75 mg. of propylthiouracil daily provides a less intense antithyroid action, as manifest by the rate and degree of the metabolic response, than the commonly used doses of thiouracil, from 0.4 to 0.6 gm. daily. Likewise the maintenance doses of propylthiouracil used have only rarely given rise to myxedema and thyroid enlargement. The clinical results have, however, been entirely satisfactory and even if it be true that larger doses would have caused a somewhat more rapid response little is to be gained from such a practice. It is possible that the avoidance of excessive dosage in this study has contributed to the favorable results.

#### SUMMARY

Two derivatives of thiouracil which have been found to be approximately ten times as active as thiouracil in animal tests have been used for the treatment of hyperthyroidism. Fourteen patients were treated with 6-ethylthiouracil; eight of these and 29 others were given 6-*n*-propylthiouracil. The only side effect encountered was a single instance of an urticarial reaction from the ethyl derivative. It was estimated that 25 mg. propylthiouracil at eight or twelve hour intervals is an adequate dose to restore metabolic equilibrium and that this state can be maintained by a daily dose of 25 to 50 mg. It is concluded that these compounds are about five times as active in man as thiouracil and are superior to thiouracil in the treatment of hyperthyroidism.

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## SOME OBSERVATIONS ON THE QUESTION OF HYPOPARATHYROIDISM OF DIENTEPHALIC ORIGIN

TO THE EDITOR:

THE PAPER of Nahum J. Winer on "Hypoparathyroidism of probable encephalopathic origin" in the *Journal of Clinical Endocrinology* 5 (2): 86-91 (1945) induces me to add the following remarks:

Winer reports on a fundamentally important case of hypoparathyroidism with encephalographic evidence of cerebral damage particularly within the hypothalamic area. He says, "This appears to be the first instance of hypoparathyroidism coincidental with apparent organic cerebral pathology." I should like to draw the author's attention to an article<sup>1</sup> of mine which appeared in 1928, and which obviously slipped his attention. This article dealt with the case of a girl, aged 20, who was suffering from both tonic seizures and disturbances to be referred to the diencephalic area. Three years prior to the onset of the tetanic manifestations the patient had had encephalitis lethargica. Apparently the hypothalamic lesion was attributable to the preceding encephalitis, and on its part had given rise to the outbreak of tetany. In the following I shall produce a brief description of the case history as given in my first report in the *Medische Klinik*. Vide also the reference to the cerebral form of tetany," as I termed it in my text-book, *The Diseases of the Endocrine Glands*, London, E. Arnold, 1935, 240; and 1944, p. 234.

The young girl in question was twenty years old. The family history and past history were negative. Three years earlier she had contracted encephalitis lethargica, as the re-

sult of which she had a bilateral reflex immobility of the pupils. Metabolic changes, pointing to a post-encephalitic hypothalamic lesion, were disturbances of the water and salt metabolism, resulting in a complete sodium chloride retention, and also a markedly low N-turnover, indicating a disturbed protein metabolism in the direction of the experimental findings of Leschke and Schneider who produced a damaging effect on protein metabolism through irritation of the diencephalon (these observations were confirmed by Freund and Grafe).

For three years, i.e., since the encephalitis, the patient had a fever (axillary temperatures up to 38° C.), indicating a disturbance of thermal regulation. Accordingly a post-encephalitic lesion in the region of the tuber cinereum or of diencephalic centres above the tuber had to be suspected.

Investigation of the patient's blood chemistry revealed most striking fluctuations of calcium, potassium, magnesium, and sugar as well as of the dry blood residues from the normal average, a condition which might almost be termed "ataxy of the metabolism." For example, the blood serum calcium varied between 7 and 12 mg. per cent. After lumbar puncture the calcium value dropped from 11.5 to 7.4 mg. per cent; the composition of the spinal fluid was practically normal and its pressure only insignificantly raised. In view of the fact that the calcium showed a definite tendency to fall to low values found with both latent and manifest tetany, I assumed that in certain circumstances the disturbed calcium regulation might even give rise to genuine tetanic seizures. As mentioned above the patient did not only exhibit metabolic changes, but also had pronounced irregularities of her body temperature, and almost behaved like a poikilothermic and not a homeothermic individual. Whenever she

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<sup>1</sup> Gedanken und Erfahrungen ueber Pathogenese und Behandlung endokriner Krankheiten (Tetanie, endokrinobrales Fieber, Morb Basedowii), *Med Klin* 24: 688 (1928)



was exposed to external heat, her body temperature adapted itself, and the blood calcium dropped. Once, when the patient complained of pains in the legs, and an electric heat bath was applied, her rectal temperature rose from 38 to 41°. This enormous rise in temperature resulted in a corresponding drop of blood calcium, and this produced an extraordinarily severe tetanic fit. Henceforth it was always possible to bring about latent or manifest tetany by heat application, whereas in the

intervals the patient did not even display signs of latent tetany such as Chvostek's or Trousseau's signs or increased irritability to electric stimulation.

I think that this history yields sufficient evidence to assume a direct relationship between the tetanic seizures to a diencephalic lesion of post-encephalitic origin.

HERMAN ZONDERMAN

*The Bikkur Cholim Hospital  
Jerusalem, Palestine*



# ANNOUNCEMENTS

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## THE SQUIBB AWARD

The E. R. Squibb & Sons Award of \$1,000.00 was established in 1939, and was given first in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, and in 1942 to Dr. Fred C. Koch. A special committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology.

## THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of endocrinology was established in 1942, but no recipient was elected due to lack of time. The work cited may be either in the field of pre-clinical or clinical endocrinology. The Award is for \$200.00. If the recipient should choose to use the Award toward further study in a laboratory other than that in which he is at present working, the Award will be increased to \$1,800.00. The option is left entirely to the recipient.

Each member has the privilege of making a nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of the nominee's most important publications, and prints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than March 15, 1946.

CARL R. MOORE, President  
HENRY H. TURNER, Secretary

## NATIONAL RESEARCH COUNCIL GRANTS FOR RESEARCH IN EN- DOCRINOLOGY

The Committee on Research in Endocrinology, National Research Council, wishes to announce that requests for grants-in-aid during the fiscal period from July 1, 1946, to June 30, 1947, will be received until February 28, 1946. Application blanks may be obtained by addressing the Secretary, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the Committee desires information regarding the proposed method of attack, the institutional support of the investigation and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses.

The Committee makes grants-in-aid of research in the general field of experimental and clinical endocrinology. However, applications for support of research in the problems of sex in the narrower sense cannot be given favorable consideration, and investigators seeking support in this field should direct their proposals to the Committee for Research in Problems of Sex of the National Research Council. The Committee on Research in Endocrinology, however, will continue to give consideration to the support of studies of the effect of sex hormones on non-sexual functions, e.g., on general metabolism and on the metabolism of steroid hormones.



# CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. Collaborators: F. A. DE LA BALZE, ISRAEL BRAM, CLARENCE D. DAVIS, ANNA F. MURRAY B. GORDON, E. C. HAMBLIN, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REIF, MEMBRIVES, A. E. MEYER, E. C. REIFENSTEIN, JR., LEO T. SAMUELS, HAROLD WOOSTER, AND J. ZANARTU.

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## PANCREAS

BRUSH, J. M.

Initial stabilization of the diabetic child. *Am. J. Dis. Child.* 67: 429-444 (1944).

The author describes in detail a regimen that he has developed since May, 1931 at New York Babies Hospital for treating previously untreated juvenile diabetic patients. He cites the results obtained by this regimen in 39 patients. The author summarizes his hypothesis and regimen as follows. Children with diabetes mellitus who have had no previous treatment are capable of recovering an appreciable capacity to regulate the level of blood sugar regardless of the severity of the symptoms when treatment is commenced, provided the therapeutic regimen is directed toward the administration of insulin in such amounts as temporarily to relieve the islet apparatus of any contribution to the total insulin needed by the organism. The characteristic of submitting to the action of large and predictable amounts of exogenous insulin regardless of the apparent clinical severity of the disease has been termed insulin acceptance. Since maximal recovery, in terms of the amount of insulin required after stabilization, is achieved only when large amounts of insulin are administered during periods of regulation and recovery, the beneficial role of therapeutically administered insulin is readily conceived in terms of substitution of the hypodermic injection for the productive effort of an exhausted islet system which, though temporarily incapacitated, can be expected to recover a large fraction of its original competence provided it is not constantly goaded by the driving stimulus of hyperglycemia. Such substitution at a constant level constitutes insulin acceptance by the diabetic child as a probable total replacement mechanism. The regimen described is applicable to children of all ages and in a wide range of clinical states and provides a practical working guide which by standardizing therapy

affords an opportunity for comparing one with another; under favorable conditions a great majority of patients respond to it with striking uniformity. The patient is given a diet calculated on the basis of his age and weight so chosen is held constant during the period of intensive treatment with insulin and not altered according to his appetite. Hunger develops during the adaptive period, after disappearance of significant glycosuria, and only represents a symptom of hypoglycemia rather than a true need for more food. After an interval of six to ten days during which the patient's daily requirement of insulin remains fairly constant at a high level (circa 60 to 70 units per 100 grams dietary fat), moderate or severe shock marks initiation of the period of functional recovery. From this point on the rate of recovery as measured by the decrease in the daily requirement of insulin, is so uniform as to be a fairly predictable in the majority of instances. The similarity of clinical course, amounting to the reproducibility of therapeutic results, suggests the operation of physiologic and chemical laws. The amount of insulin administered is decreased at a prescribed rate, which is calculated to steer the patient through the relatively narrow channel between glycosuria and insulin shock during the ensuing days of improving tolerance to carbohydrates and diminishing requirements of insulin. Mild shock, which is rarely disturbing to the child and never actually harmful, serves to indicate that enough insulin is being given. Improvement, once it has set in, may be terminated if the daily dose is reduced abruptly because of the occurrence of insulin shock; one loses ground by attempting to reduce the amount of insulin used as an end in itself. After hospitalization for 22 to 30 days the patient is ready to be cared for at home, free from glycosuria, essentially free from shock and in a fair state on a full maintenance diet controlled by a single daily injection of insulin of between ten and eight units. This regimen is not expected to

long term result in these patients, and it is recognized that within a year or two after the onset of symptoms most patients will come to require more than 30 units of insulin a day, and any of them far more, regardless of the method which they are treated in the early months after the onset. However, the author contends that his regimen, by contrast with a number of other methods of treating diabetic children, possesses certain advantages in that it holds the patient under close observation until he has reached a steady state, in that within this limit it confines him to the hospital a minimal length of time and in that it stabilizes his requirement of insulin at the lowest level compatible with efficient metabolic economy.—*E.C.R., Jr.*

ENGELHARDT, H. T., AND V. J. DERBES

Tumefaction of subcutaneous fat following the injection of insulin. A chemical and histologic study. *Am. J. M. Sc.* 207: 776-781 (1944).

In a 12-year-old child tumefaction of both subcutaneous fat deposits, three years of age, had increased slowly in size for six years. A mass of material histologically indistinguishable from normal fat was removed by biopsy. Detailed chemical analyses of this material and of fat tissue removed from the abdominal pannulus of an individual who had met sudden death were compared. There was very little difference in the non-diabetic and diabetic patients except that the diabetic fat was higher in un-saponifiable matter and phosphatids. The authors favor the hypothesis that the phenomenon of tumefaction is due to a local physiologic stimulatory effect of the insulin, with localized fat retention.—*E.C.R., Jr.*

ANDERSON, M. B.

Factors influencing the return of tolerance for glucose in middle-aged obese diabetics. *Am. J. M. Sc.* 208: 15-24 (1944).

An analysis was made of the carbohydrate tolerance of 55 ambulatory diabetics reporting to the Long Island College Hospital, following dietary management. All of the patients were markedly obese and over 40 years old at the onset of the diabetes. In the analysis, the blood sugar levels, the response to the oral glucose tolerance test of Exton-Rose and the change in weight were evaluated. They conclude that: 1) obese patients who are over 40 years of

age when glycemia and hyperglycemia first appear should be treated at once by strict dietary restriction aiming for reduction in weight, for disappearance of glycosuria and for a physiologic blood sugar level; 2) when such a regime is followed a remarkable return of tolerance to carbohydrate may occur; 3) to induce such a return of tolerance strict cooperation of the patient in following the diet is imperative; 4) when dietary management is not instituted in such patients until they have lost weight from neglect of treatment, ability to regain carbohydrate tolerance becomes permanently impaired; and 5) obese patients who have neglected treatment for many years are very difficult to manage unless they can be induced to lose weight by following a dietary regime. The authors believe that a kinetic viewpoint must be maintained toward these cases. The most important factors diminishing the ability of a patient to regain carbohydrate tolerance are: 1) lack of proper weight reduction; 2) delay over a period of years in treating the patient; 3) poor cooperation by the patient in following the weight-reducing regime; and 4) onset of the diabetes at an early age.—*E.C.R., Jr.*

KENNEDY, W. B., AND F. D. W. LUKENS

Alloxan diabetes. *Am. J. M. Sc.* 207: 550 (1944).

Rabbits were made diabetic by the intravenous administration of alloxan (200 mg. per kg. body weight). Ten animals which survived exhibited moderately severe diabetes (blood sugars ranged from 300 to 700 mg. per cent). Between 15 and 70 per cent of the calculated available dietary glucose was excreted in the urine; but the nitrogen excretion of the fasting diabetic rabbits was not significantly increased over that in the normal rabbit. The islands of Langerhans showed early widespread necrosis which progressed to atrophy. Although an elevated blood urea nitrogen was found at death in two rabbits, renal lesions (observed by others) were absent.—*E.C.R., Jr.*

LERMAN, J.

Insulin resistance. The rôle of immunity in its production. *Am. J. M. Sc.* 207: 354-360 (1944).

The blood from six patients with insulin resistance was examined by one or more of the following tests: a) ring precipitin, b) passive transfer, and c) biologic antagonism and was found by one or more of these tests to contain insulin antibody.

ies. The author concludes that: 1) antibodies to insulin appear to be antihormonic, 2) insulin resistance is dependent upon the appearance and concentration in the body of antibodies to insulin, 3) the return of normal insulin sensitivity is dependent upon the disappearance of the immune response, 4) the repeated administration of insulin, rather than its omission, offers a means for overcoming insulin resistance, 5) antibodies to insulin simulate antibodies to other hormones by being hormone-specific rather than species-specific, and 6) since patients recovering from insulin resistance usually become severe diabetics requiring 50 to 60 units of insulin daily, it is suggested that this represents the level of complete diabetes.—*E.C.R., Jr.*

MARTIN, H. E., D. G. SIMONSEN AND N. H. HOMANN

Time-activity curves of globin insulin with clinical applications. *Am. J. M. Sc.*, 208: 321-332 (1944).

From studies on 36 patients the authors make the following observations concerning globin insulin: 1) the duration of action (dose of 10 to 80 units) varied with the dose and the severity of the diabetes, but in general was 14 to more than 24 hours—average 18 to 19 hours; 2) the peak of activity occurred between the 6th and the 10th hours; 3) the activity began within one hour of injection but increased slowly for the first three to five hours; 4) the time-activity function for a given dose was intermediate between regular and protamine zinc insulins as to duration and to total carbohydrate-handling ability; 5) the most satisfactory control of the blood sugar level of 14 patients receiving globin insulin (? in the morning) occurred when the patients were given a light breakfast, a mid-afternoon feeding, and in some instances a bedtime feeding; 6) globin insulin maintained fair to good control (except for occasional upsets) of the majority of 16 outpatients; 7) globin insulin has the following advantages: a) it allows better control of patients who are having severe nocturnal reactions with protamine zinc insulin, b) it allows better control of patients who are receiving before breakfast both regular and protamine zinc insulin (injected singly or combined), c) it has more carbohydrate-handling ability than protamine, with an earlier peak of action, and d) it is a clear solution which obviates mixing; and 8) globin insulin has the following disadvantages: a) it has

too low an hourly carbohydrate-handling to cover the diet in most severe diabetics; b) it has too short a duration of effect to cover the nocturnal insulin requirement of severe diabetics, and c) in an obese patient it causes burning when injected.—*E.C.R., Jr.*

MILLER, H. C., R. D. JOHNSON AND S. H. LACHER

A comparison of newborn infants with erythroblastosis fetalis with those born to diabetic mothers. *J. Pediat.* 24: 603-615 (1944).

The histories and clinical data of 20 infants born to diabetic mothers at the New Haven Hospital, the Boston Lying-in Hospital and the New York Hospital are compared with the data of 36 infants with erythroblastosis fetalis studied at the New Haven Hospital. The somatic and visceral changes are similar: an increased reticulocyte count, blastemia, extensive extramedullary erythropoiesis, an hypertrophy of the heart, hyperplasia of the islets of Langerhans, adrenal enlargement, edema, macrosomia, and a tendency to hemorrhage in all the tissues of the body. Two significant differences between the two groups were found: 1) infants with erythroblastosis fetalis frequently have anemia and jaundice and the Rh factor of the mother's blood is negative; whereas, infants born to diabetic mothers rarely have anemia and jaundice and the distribution of the Rh factor among their mothers is similar to that in the population at large. The relationship of the Rh factor in the mother to the similarities and differences in the two groups of infants is discussed.—*E.C.R.*

OPPENHEIMER, M. J., AND F. C. MANN

The intralobular pancreatic circulation. *Gastroenterology* 3: 218-226 (1944).

Casts of the circulation of the pancreas in dogs, cats, rabbits, guinea-pigs and white rats were made by intra-arterial injections of a mixture of prene or neoprene mixtures followed by perfusing with alcohol and the digestion of extralobular tissue with hydrochloric acid. The cast of the bed was so great that the cast of the vascular bed thus obtained resembled the intact organ very closely when seen macroscopically. Without anastomoses were noted between acinar capillaries and also between recipient capillaries and the islets, thus insuring "adequate circulation under varying circumstances." Islets varied considerably in size and were placed entirely on the

ial side of the circulation. Blood may reach the cini directly or by way of the islet tissue, as dissections beginning at the interlobular arteries and ending at the intralobular capillaries have shown.—*T.H. McG.*

## PARATHYROID

OBURN, D. E.

Severe osteitis fibrosa cystica with parathyroid tumor; report of case of 15 years' duration. *Am. J. Surg.* 66: 252-258 (1944).

A severe case of generalized osteitis fibrosa cystica due to parathyroid adenoma is reported, the tumor being located in the superior mediastinum. The case is remarkable in that the patient's symptoms date back over a period of nearly sixteen years during which time she suffered no less than four fractures and one operation for kidney stones. The skeletal involvement is extensive and included both patellas, a site which has not been previously reported. Her postoperative convalescence was marked by a fracture of the right femur, suggesting that in the postoperative care of these patients precautionary splinting might be applied to bones of the extremities which are extensively involved until some degree of recalcification has occurred. *Author's Summary.*

## THYROID

AM, I.

Thyroid disease in youngsters under age sixteen; comments on a series of 1,200 cases. *Arch. Pediat.* 61: 300-310 (1944).

During a period of 33 years, the author has observed a series of nearly 17,000 cases of thyroid disease, of which approximately 1200 (7%) occurred in children under age sixteen. The author gives a general account of the disease in children and concludes: 1) The disease (with and without fever) differs from that in adults; treatment also differs since surgery is rarely required. 2) Differential diagnosis of thyroid disease in children is not easy since many conditions to be excluded (e.g. paroxysmal tachycardia, anemia, anxiety neurosis, undernutrition, primary heart disease, anemia, intestinal parasites) alter the basal metabolic rate, and since congenital defects (cysts or "pop-eyes") may be present. 3) Hypothyroidism and hyperthyroidism are not necessarily associated with goiter, and vice versa. 4) The etiological factors in simple sporadic goiter in children

are heredity, faulty dietetic and hygienic habits, local or general infections, and a singular incapacity of the thyroid to meet the requirements of growth and development. 5) Once discoverable etiological factors are eliminated, the specific medicament of hypothyroidism and sporadic simple goiter in children is not iodine but thyroid substance. 6) The hyperthyroidism of exophthalmic goiter (Graves' disease) is not due to goiter but to a constitutional neuroendocrine dysfunction in which the thyroid gland is not etiologically, but sequentially implicated. The etiological factor in the average case appears to be a congenital predisposition (Graves' constitution) upon which is superimposed an exciting cause in the form of a psychic trauma, an infection, continued tension or overwork. 7) Since exophthalmic goiter is a psychosomatic syndrome, psychotherapy is a major factor in treatment within a broad regime of patiently applied therapy.—*E.C.R., Jr.*

BRUCH, H., AND D. J. McCUNE

Mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment. *Am. J. Dis. Child.* 67: 205-224 (1944).

The authors have examined the effect of adequate treatment with thyroid hormone as judged by physical progress on the mental development of congenitally hypothyroid children. Their evaluation is based on a review of the literature and on longitudinal studies of 23 children (7 boys and 16 girls) who attended the Vanderbilt Pediatric Clinic of the New York Babies Hospital. These children were selected on the basis of: a) adequate data for appraisal, b) unequivocal diagnosis based on physical response to thyroid hormone treatment and its withdrawal. Determinations of skeletal height, bone age, serum cholesterol and urine creatine were found to be of value in making the diagnosis. Retardation of bone age of more than six months was present in only five cases at the time their mental status was determined. Thirteen children were under one year of age, the youngest was three months of age, four children were between one and three years of age, and six were more than three when therapy was started. Mental development of these patients was evaluated by psychometric testing at intervals. Two patterns of progress were observed: 1) development following closely the lines of expected

progress; and 2) arrest of development at a low level. Physical development, particularly skeletal maturity, was related to the age at the beginning of and the adequacy of treatment; mental development, on the contrary, progressed more or less independently of treatment and tended to become arrested in children of low intelligence. Six cases are presented in detail. The authors conclude: 1) although there is a distinct relation between early, adequate treatment and subsequent physical development, a comparable relation is absent, or at most highly imperfect, with respect to mental attainment; 2) the intellectual inferiority presented by many congenitally hypothyroid children is not in all cases due to lack of thyroid hormone, but in some instances at least is due to a concomitant defect in cerebral development which cannot be modified by glandular treatment; 3) in other cases, however, retarded growth of the brain may be due to post-natal lack of thyroid, and hence early diagnosis and treatment is important; 4) the functional development of congenitally hypothyroid children before treatment supplies an index of their capacity for future mental development, since those with the capacity for good intellectual development are much less retarded than those whose subsequent progress will be poor; 5) the prognosis for intellectual development must be guarded in advance of therapeutic trial; and 6) too vigorous use of thyroid therapy can have distinctly undesirable consequences, since deterioration of performance quantitatively measurable by psychometric tests and serious disorders of behavior may occur when excessive amounts are administered.—*E.C.R., Jr.*

CHESLEY, L. C.

Observations on the absorption, apparent volume of distribution and excretion of thiourea. *J. Clin. Investigation* 23: 856-858 (1944).

In suitable normal subjects, the blood, urine, stools, and milk were analyzed for their content of thiourea at periodic intervals following a test dose of 1000 mg. of thiourea. Urea and thiourea clearances were simultaneously performed. From these data, attempt was unsuccessfully made to estimate the total body water. In the course of the experiments it was found that the renal clearance of thiourea is very close to that of urea; that thiourea enters the cerebrospinal fluid, probably slowly; that the concentration of thiourea in serum and in breast milk is nearly the

same; that when single doses of 1000 mg. of thiourea are given by mouth, about 25% cannot be recovered; and that none of the ingested thiourea appears in the feces within 5 days following its administration.—*T.H.*

CHU, J. P.

The influence of thyroid on pregnancy and parturition in the rabbit. *J. Endocrinol.* 4 (2): 109-114 (1945).

Unlike Krichesky (1939) the author found that the thyroid gland is necessary for normal gestation in the rabbit. If thyroidectomy was performed at an early stage of pregnancy, resorption and abortion of the embryos occurred while if the operation was performed at a late stage of pregnancy stillborn young were delivered. When pregnancy was induced in thyroidectomized rabbits the embryos were resorbed or aborted or prolongation of gestation resulted owing to retention of fetuses. The born fetuses of thyroidectomized animals were usually dead. Thyroidectomized rabbits with desiccated thyroid following the operation gave normal viable litters in two out of five cases. Superfecundation was successfully induced in thyroidectomized rabbits by injection of pituitary gonadotrophin immediately after coitus. The large number of embryos thus induced was usually resorbed. Resorption could be prevented by administration of desiccated thyroid started immediately after mating. The author concludes that the thyroid hormone is essential in maintaining the vitality of the embryos. The prolongation of pregnancy is assumed to be due to over-production of estradiol in the absence of the thyroid. This is thought to be due to an increase in the production of follicle stimulating hormones of the pituitary gland.—*L.T.S.*

DALTON, A. J., H. P. MORRIS AND C. S. DUNN

Changes in the organs of female C3H mice receiving thiourea. *J. Nat. Cancer Inst.* 45: 451-454 (1945).

Thiourea was added to the diet of C3H mice when they were 11 months old. The animals were maintained on this diet until they developed spontaneous mammary cancer, when they were killed and the uteri, adrenals, and thyroids studied histologically. The thyroids showed the hyperplasia, red blood cells were four times

hair follicles, and a granular, greenish yellow pigment appeared in the cytoplasm in the distal portion of the follicular cells. No changes were seen in the uteri, but a general degeneration of the follicles and ova was noted in the ovaries, and there was a decrease in the osmiophilic material of the adrenal cortices.—*Courtesy Cancer Research.*

ABRILLOVE, J. L., M. J. KERT AND L. J. SOFFLER

The use of thiouracil in the treatment of patients with hyperthyroidism. *Ann. Int. Med.* 23: 537-558 (1945).

Thiouracil was employed in the treatment of 51 patients with hyperthyroidism and in three patients with non-toxic goiter. During the first four to six weeks of treatment the patients were hospitalized and given thiouracil in a dosage of .4 to 1.0 gm. After discharge, the dosage of thiouracil was reduced to 0.1 or 0.2 gm. daily and the patients followed in the outpatient department. Thiouracil was continued for a variable length of time, the longest period of continuous treatment being ten months. Thirty-three of the patients with hyperthyroidism (29 cases of primary hyperthyroidism and four of recurrent hyperthyroidism) were treated successfully with thiouracil. Three patients with hyperthyroidism were successfully prepared for operation with thiouracil. Four patients were dismissed as showing lack of response to thiouracil. Three of these patients received the drug for no more than 30 days; in the fourth, the dosage of thiouracil had to be sharply reduced because of leukopenia after an initially favorable response, and the B.M.R. rose again. These patients were operated upon successfully after preparation with iodine. Severe toxic reactions forced the discontinuance of thiouracil therapy in 11 cases. Thirty-one per cent of the patients developed some toxic manifestation. Conjunctivitis was observed in 5 cases; edema; drug fever, 4; leukopenia, 1; and agranulocytosis, 6. One case of agranulocytosis was fatal. Liver and kidney function tests remained normal throughout the course of treatment. In the authors' opinion, the indications for the use of thiouracil therapy are: (1) Preparation of iodine-fast patients for surgery; (2) Treatment of individuals with hyperthyroidism, in whom for some reason surgery is deemed hazardous; (3) Treatment of cases of recurrent hyperthyroidism who have been operated upon twice or more.—*J.M.*

LAHEY, F. H., E. C. BARTELS, S. WARREN AND W. A. MEISSNER

Thiouracil—its use in the preoperative treatment of severe hyperthyroidism. *Surg., Gynec. and Obst.* 81: 425-439 (1945).

Clinical observations on 190 severely hyperthyroid patients prepared for operation with thiouracil are reported. It was found that approximately one day of treatment with 0.6 gm. of thiouracil was required for each percentage of elevation in the basal metabolic rate. Patients treated previously with iodine required a slightly longer period of treatment to return the metabolic rate to normal. Patients whose hyperthyroidism was of no more than two to three months' duration responded more quickly to treatment than did those whose disease had been present for a longer time. In the earlier patients prepared for operation with thiouracil alone, a troublesome surgical complication was encountered. The thyroid gland proved to be extremely friable, rendering hemostasis so difficult that it was sometimes impossible to do a sufficiently radical thyroidectomy. This difficulty was overcome by administering iodine during the three week period immediately before operation. For two weeks iodine and thiouracil were administered simultaneously and during the final week iodine alone was given. In patients adequately treated with thiouracil the pulse and blood pressure remained constant during operation, and postoperative reactions did not occur. Toxic reactions developed in 11% of the patients. These consisted of: granulocytopenia, 9 patients; fever, 7; skin eruption, 4; sclerodema, 2; and swelling of the salivary glands, 1. Four of the patients with granulocytopenia developed agranulocytic angina and one patient died. Seventy-seven glands resected from this group of patients were subjected to pathological study. It was not possible to distinguish a thiouracil-treated specimen from a hyperplastic gland which had no previous thiouracil therapy. When iodine was used in conjunction with thiouracil the majority of specimens showed histologic evidence of involution.—*J.M.*

PUPPEL, I. D., H. T. GROSS, E. K. MCCORMICK AND E. HERDLE

The rationale of calcium, phosphorus and vitamin D therapy in clinical hyperthyroidism. *Surg., Gynec. and Obst.* 8: 243-265 (1945).



Besides an extensive review of the pertinent clinical and experimental literature, the authors present studies on the effects of calcium, phosphorus and vitamin D therapy on the calcium balance of 11 patients suffering from hyperthyroidism. An average loss of 459 milligrams of calcium per day occurred in these patients maintained on a low calcium intake (averaging 474 mgm. per day over a period of 90 days). A positive calcium balance averaging 352 mgm. per day was achieved in the patients given an adequate intake of calcium from various sources (averaging 2410 mgm. per day over a period of 81 days). Retention occurred whether the calcium was fed or given parenterally. Similar changes occurred in the phosphorus balance. Calcium gluconate, calcium lactate with drisdol, intravenous calcium chloride, and dicalcium phosphate with viosterol were adminis-

tered to groups of patients as supplements to the high calcium and high phosphorus diet. All proved effective in maintaining retention of calcium and phosphorus, but dicalcium phosphate with viosterol promoted 200% greater retention than did any of the other forms. The ordinary hyperthyroid patient requires about two grams of calcium per day to maintain positive calcium balance. This is at least twice the optimal calcium requirement of normal adults. Three grams daily is a more adequate amount to restore depleted calcium. Phosphorus requirements are similarly increased. The authors have been impressed by the smooth postoperative course and absence of thyroid storms exhibited by their patients who have received adequate calcium, phosphorus and vitamin D in addition to the older preoperative regimen.—*J.M.*



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<sup>1</sup> Harrington, C. R.: "The Thyroid Gland," Oxford, 1933, p. 141.  
<sup>2</sup> Meyer, A. E., and Wertz, A.: Endocrinology 24 806, 1939.

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# The Journal of CLINICAL ENDOCRINOLOGY

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## THERAPY WITH AQUEOUS SUSPENSIONS OF TESTOSTERONE

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**T**REATMENT of hypogonadism in males has been carried out with testosterone propionate and with methyl testosterone. The pure steroid, testosterone, has been used also in pellet form by implantation. Recently aqueous suspensions of estrogenic steroids have been employed in treating women in the climacteric. A trial of a similar suspension of pure testosterone was undertaken. The preparation used contained 20 mg testosterone in 1 cc, and was furnished in sealed glass ampoules. Prior to removal into the syringe for intramuscular injection the content of the ampoule was agitated vigorously by hand to assure a uniform suspension. No pain was experienced by the patients, and no local reactions were observed. Patients learned with ease to make their own injections. The results are illustrated herein by reports of a series of five men who were treated for hypogonadism due either to a delayed development or to the climacteric.

*Case 1, D F, Wis Gen Hosp No 126402 aged 18 was referred because of delayed adolescent development which had led to his rejection by the Selective Service Board. He had been unstable in school and unable to hold employment. He showed no development of facial, axillary or pubic hair, and the genitalia were preadolescent in size and type. His actions were spoken of as juvenile or feminine. Height was 162 cm weight 51 kg blood pressure, 96/70 mm Hg. Physical examination otherwise was within normal limits. Basal metabolic rate was plus 24 per cent, serum cholesterol 188 mg per*

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<sup>1</sup> Present address: Hoffman, LaRoche, Inc., Nutley, N J

\* Grateful acknowledgment for a supply of testosterone suspension is made to Mr P E Sprague of the Glidden Co., and Dr C Neilsen of the Abbott Laboratories

100 cc. X-rays showed the femoral epiphyses ununited; bone age was estimated at 14 $\frac{3}{4}$  years. The sella turcica was slightly small. No gonadotrophic hormone could be found in two, twelve hour, night urine specimens.

The patient was treated with anterior pituitary growth promoting extract<sup>3</sup> hypodermically in doses of 1 cc. daily for four months without showing a definite increment of growth. When re-examined one year later his height was 165 cm.; weight, 54 kg., and there was no other important change in either history or physical examination. He was treated next with equine gonadotrophic hormone,<sup>4</sup> receiving 70 doses of ten units in each dose on alternate days, without obvious result. Subsequently he was treated with anterior pituitary gonadotrophic hormone,<sup>5</sup> receiving 25 Hisaw-Fevold units daily for 100 doses. No obvious benefit occurred.

Following this the therapy was changed to an aqueous suspension of testosterone,<sup>6</sup> in doses of 20 mg. twice weekly for nine weeks. He developed a more mature attitude and a more definite interest toward girls. He secured and held steady employment, and on reexamination three months after stopping therapy, the penis had enlarged somewhat, the prostate was firm and palpable, a slow growth of hair had shown itself on his face and pubic areas, and he reported an increased frequency of erections. Throughout the entire period of treatment there had been a very gradual deepening of the register of the voice which had become typically adult at the last examination.

*Case 2, H.T., Wis. Gen. Hosp. No. 117736*, was referred at the age of 53 because of fatigue which interfered seriously with his work as a veterinary. He had epigastric discomfort, bloating, and felt the need for eating between meals because of his fatigue and weakness. He complained also of dyspnea, paresthesias, a marked reduction in libido, and of premature ejaculations. Glycosuria had been found but was demonstrated to be an emotional hyperglycemia and glycosuria, with normal sugar tolerance test. Test of renal capacity for excreting potassium and retaining sodium definitely eliminated adrenal insufficiency. Physical examination was remarkable only in showing a soft left testicle with scarred left epididymus. Blood pressure was 106/74 mm. Hg.; weight, 75 kg.

He was treated with testosterone propionate in oil, 25 mg. intramuscularly, at intervals of three times weekly, decreasing gradually to once weekly, with very distinct benefit. A change was made to the use of testosterone ointment, 25 mg. being introduced by inunction once weekly. The results were not satisfactory. Therapy was changed to methyl testosterone, 10 mg. orally daily, and did not feel satisfied with the results. He returned to the use of testosterone propionate 25 mg. every three days and was well satisfied for many months. Subsequently therapy was changed to aqueous suspension of testosterone, 20 mg. being injected intramuscularly once weekly. After a year on this routine he reported that he felt entirely comfortable so long as he took his medication. Intervals longer than one week were definitely associated with return of his previous symptoms. Blood pressure was 120/70 mm. Hg., and his weight had gone up during the program on aqueous testosterone from 75 kg. to 83 kg. while he continued with his usual veterinary work.

*Case 3, L.W.F., Wis. Gen. Hosp. No. 223662*, was referred at the age of 46 because of weakness, vertigo, decreased libido, marked morbid melancholy with frequent weeping

<sup>3</sup> *Phykentrone*, (Squibb).

<sup>4</sup> *Gonadogen*, (Upjohn).

<sup>5</sup> *Gonatropo*, (Straub).

<sup>6</sup> (Abbott).

for about four years, irritability, and hot flashes. He had a tendency to worry that he was becoming insane, and complained of subjective inadequacy to continue with his employment. Past medical history included a thoracotomy for empyema with good results. Physical examination showed weight, 66 kg.; blood pressure, 104/76 mm. Hg.; and he had a low grade chronic prostatitis.

Assay of 12 hour, night, urine specimens for gonadotrophic hormone showed no definite increase compared with normal levels, i.e., he did not present the hormonal change characteristic of the climacteric.

He was treated with prostatic massage and chemotherapy and was given aqueous suspension of testosterone, 20 mg. daily for five doses, and then the same dose twice weekly. Marked subjective improvement occurred although the relief from the prostatitis was only gradual. By his own criteria he found that injections were necessary at intervals of not more than four days. When the interval became five days or longer there was a return of all the previous symptoms. Blood pressure was 116/88 mm. Hg. Weight rose, without attempt at dietary change, to 73 kg., and he was able to return to steady employment. Therapy was changed to the use of methyl testosterone, 10 mg. daily orally, and subjective benefits were maintained.

*Case 4, E.K., Wis. Gen. Hosp. No. 242671*, was seen at the age of 51, complaining of fatigue, weakness, hot flashes, sweating, dyspnea on exertion, nervousness, paresthesias, headaches, and a sense of epigastric fullness and constipation. With a height of 187 cm., his weight of 96 kg. represented a moderate obesity of long standing. Physical examination showed slight sclerosis of retinal vessels, a soft systolic murmur at the apex, a blood pressure of 108/76 mm. Hg., and no other significant abnormal findings. The patient complained of distinct decrease of libido within the past year. Laboratory findings were within normal limits. He was treated with aqueous suspension of testosterone, 20 mg. twice weekly for two weeks and thereafter once weekly. No dietary limitations were attempted. He gained 6 kg. and at the end of two months reported he was markedly improved so far as all his complaints were concerned. He was provided with sufficient material to continue treatment at 10 day intervals for three months.

He did not return until seven months later by which time he had discontinued therapy and his previous symptoms had returned. Because of his complaint of dyspnea on exertion attention was directed chiefly to his heart by the physician who examined him. Electrocardiogram at this time (not previously taken) was reported as indicative of advanced myocardial degeneration probably on a coronary sclerotic basis, with auricular and nodal premature contractions. He had no physical signs of congestive failure. We did not learn of his return to the hospital. He was not given further testosterone but was advised to reduce weight and to use aminophyllin 200 mg. four times daily.

*Case 5, H. K., Wis. Gen. Hosp. No. 129438*, was seen at the age of 63 complaining of fatigue, polyphagia, polydipsia, polyuria, nocturia, loss of 6.5 kg. in one month, drowsiness, somnolence and occasional cramps in the calves. There had been mild vertigo for a year, slight dyspnea and cardiac consciousness after exercise. Physical examination was not remarkable except as follows: blood pressure was 140/70 mm. Hg.; liver was distinctly enlarged with the border at about the level of the umbilicus; the spleen was enlarged to about five cm. below the costal border and slightly tender. The skin was dry. With glycosuria and the blood sugar of 350 mg. per cent, a diagnosis of diabetes mellitus was obvious. Treatment was carried out with a weighed diet, supplemented with protamine insulin. Distinct clinical improvement followed.

During subsequent months he developed insomnia and had a rather poor endurance



for muscular exercise to which he had been accustomed. He noticed paresthesias in the legs, hot flashes, choking sensations, occasional palpitation, a morbid tendency to feel discouraged and to lack enthusiasm for his usual occupations or for friendly contacts. Libido had disappeared. Physical examination showed regression of the hepatomegaly and splenomegaly toward normal limits. Rectal examination showed slight hemorrhoidal dilatation and the prostate was tender but not enlarged.

Eight months after beginning therapy for diabetes and at the time when the diabetes was under strictly good control therapy with methyl testosterone, 10 mg. daily orally was started. An increase to twice daily caused occasional erections, some improvement in muscular endurance but no improvement in mental symptoms. An increase to 30 mg. daily caused further distinct improvement without libido, however. After four months therapy was changed to aqueous testosterone, 20 mg. daily intramuscularly. He found prompt and lasting benefit from this therapy, deciding at first on an interval of from five to seven days between injections. He was more comfortable than on oral methyl testosterone. Libido was not significantly increased, erections were not bothersome, and he was essentially free from symptoms. This therapy was continued for 12 months with the interval usually four days between injections. On longer intervals the previous symptoms began to return after the fifth day. With such therapy this blood pressure varied from a maximum of 160/86 mm. Hg. to minimum of 145/90 mm. Hg., and was 150/90 mm. Hg. when he was two weeks without therapy. No essential change occurred in the management of the diabetes under hormone therapy.

## DISCUSSION

*Case 1* shows typical refractory testes which respond poorly to gonadotrophic therapy, and in this situation substitution with testosterone offers the only prospect at present of clinical benefit, granting that there is no probability of establishing fertility. It is known that testosterone propionate or methyl testosterone will induce a growth of the penis and the accessory organs, as well as the development of the secondary sex characteristics. The same goal can be achieved by use of aqueous suspension of testosterone crystals. The dose and the interval between injections must be determined by observation of the rate of progress in any case, as with other preparations.

*Cases 2 to 5* are clinically typical of the climacteric syndrome in males. Comparisons of aqueous testosterone with the other methods of treatment are possible in *Cases 2 and 5*. The benefits are equally good with either the aqueous suspension or the oil solution of the propionate. The time interval from one injection until the subjective need for another was about the same with either preparation, viz.: one week in *Case 2* and from four to five days in *Case 5*. It has been possible to provide relief from the mental and autonomic symptoms without advancing the dose to a level which causes frequent erections or distinct increase in libido. These results have followed use of larger doses in other patients we have treated with testosterone propionate.

In *Case 3* the lack of gonadotrophic hormone increase in the two, night,

urine samples examined raises a question of the truly climacteric nature of the syndrome. Although we agree with the experience reported by Heller and Myers (1) that gonadotrophic hormone excretion is regularly increased in the climacteric, we can suggest merely that this patient had the symptoms and responses characteristic of the male climacteric. The occurrence of a chronic prostatitis in the climacteric is frequent enough so that we consider it a sequel to reduced testicular stimulation of the prostate rather than a cause of the symptoms.

In *Case 4* we regret the inability to continue the observations, but hope that after a trial of vasodilator therapy it may be possible to undertake a second course of testosterone to decide whether the response is again as good as before. It is well known that testosterone has provided subjective relief for men with anginoid pains. The effects have been thought due to coronary dilatation and improved myocardial status.

#### SUMMARY

An aqueous suspension of testosterone crystals injected intramuscularly in doses of 20 mg. provides a satisfactory replacement therapy in male hypogonadism. The apparent period of effective supply of testosterone from each injection is from four to seven days.

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1. HELLER, C. G. and G. B. MYERS. The male climacteric: its physiology, symptomatology, diagnosis and treatment. *J. Clin. Investigation*. 21: 622 (1942).



# DIETHYLSTILBESTROL IN AQUEOUS SUSPENSION

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A LARGE proportion of the preparations of sex hormones, both male and female, which are intended to be administered parenterally are dissolved in vegetable oil. While therapy with these preparations is both practical and satisfactory, there is a disadvantage to their administration in the fact that due to the oil vehicle there is a significant incidence of allergic or irritating action at the site of injection. These local reactions are not infrequent, and depend upon the type of vegetable oil used as a vehicle. The oils customarily used are derived from sesame, peanut or corn, and the incidence of reactions due to some of these oils may amount to 20 per cent. Sesame oil seems to be the least allergenic. Induration, itching, bleb formation and swelling of the neighboring tissues may be slight after the first or second injection, but they may become increasingly severe and may cause significant disability and pain for relatively long periods of time. Occasionally a patient will respond to the first injection with a severe reaction. Sevringhaus has pointed out repeatedly the need for a medium other than oil.

We have already reported our employing injections of estrone crystals suspended in aqueous medium in order to obtain freedom from allergic reactions (1). This preparation, now available commercially, has proven satisfactory not only from this standpoint, but also because of its increased effectiveness over estrone dissolved in oil. This increased effectiveness is probably due to a slower rate of absorption of the estrone crystals from the site of injection, since, following the rapid absorption of the aqueous vehicle, the crystals of estrone behave like small implants which are more slowly absorbed from the tissues than the oil solution. We have therefore extended our experiments with aqueous suspensions of fat soluble hormones to another commonly used estrogen, diethylstilbestrol.

This well known synthetic estrogen is potent and inexpensive. Its usefulness is however curtailed because it induces a relatively high incidence of side reactions such as nausea, vomiting, dizziness, etc., and this occurs when the material is administered by injections as well as by mouth. We have shown that this high incidence of unpleasant reactions is due to its rapid absorption into the blood stream, and that these toxic symptoms are the result of physiologic changes in the tissue, much like those which occur in early pregnancy where the symptoms are similar. When the absorption

into the blood stream is delayed by combining diethylstilbestrol with fatty acid esters such as propionic and palmitic acid, the incidence of these disagreeable reactions decreases (3). If it could be demonstrated that the aqueous suspension of diethylstilbestrol has likewise a slower absorption than that dissolved in oil, we would then have the advantages of decrease in toxicity, improved therapeutic action and freedom from the allergic reaction of the oil vehicle.

### METHODS AND RESULTS

Two groups of menopausal women with typical symptoms of a moderate to a severe degree received by injection the preparation of diethylstilbestrol suspended in water. The injections were administered every two weeks and the doses were 2.5 mg. and 5 mg. The degree of relief from the symptoms was evaluated as three plus for excellent relief; two plus, moderate relief; one plus, slight relief; and 0, no relief. The use of menopausal patients for testing the potency of the following estrogens has already been described by us: estrone in aqueous suspension (1), diethylstilbestrol and its esters (3), estrone sulphate (4), hexestrol (2) and benzeestrol (5).

Therapeutic Effect on Menopausal Syndrome of Diethylstilbestrol in Aqueous Suspension Administered at Two Weeks' Intervals

2.5 mg.		5 mg.	
No. of patients	Degree of relief	No. of patients	Degree of relief
36	+++	28	+++
64	++	20	++
6	+	3	+
5	0	2	0
—		—	
101		53	

From the above tables it can be noted that diethylstilbestrol in aqueous suspension controls satisfactorily menopausal symptoms in the majority of women when injected at the relatively infrequent interval of every two weeks. The relief of these patients is similar to that obtained from the use of most of the commonly accepted estrogens, including the natural ones. The incidence of side reactions in the above series of cases were as follows: four of the 101 patients who received the 2.5 mg. dosage complained of nausea for from one to two days, and two of the 53 patients who received the 5 mg. dosage had similar symptoms over a similar period of time. The intensity of these reactions was not as severe, however, as that of many patients who have taken 1 mg. of diethylstilbestrol orally for only a few days.

This incidence of toxicity is considerably less than that demonstrated by patients who have received diethylstilbestrol in oil, as shown by the fact that 15 out of 32 patients who received 5 mg. of diethylstilbestrol in oil developed the severe nausea, vomiting, *etc.* (5). This would indicate that the absorption of crystals of diethylstilbestrol in aqueous medium is sufficiently delayed to prevent the sudden rise of blood estrogen which is responsible for the development of the untoward symptoms. While no claims are made here as to the greater potency of the material when placed in aqueous suspension, the fact that there is an increased effectiveness wherever this material is treated to delay its absorption, would indicate that its potency might be appreciably increased. Certainly we have little hesitation in using the aqueous suspension when compared with the trepidation felt upon administering the same material in oil. In addition to the increased usefulness of diethylstilbestrol when it is administered in the aqueous suspension for therapeutic purposes, its freedom from local allergic reactions, encountered rather frequently with the oil solutions, gives it an added value. Physicians should find this new dosage form a probably more effective preparation than that which is in use in the form of the oil solutions, but definitely safer from the standpoint of systemic toxicity and local irritation.

#### SUMMARY

1. Diethylstilbestrol in aqueous suspension is a satisfactory estrogen when administered to menopausal patients.
2. It induces a relatively low incidence of unpleasant reactions such as nausea, vomiting, *etc.*
3. This preparation possesses the further advantage of being free from substances that induce the local allergic reactions encountered with oil solutions.

The preparation of diethylstilbestrol crystals in aqueous suspension was furnished by Abbott Laboratories, North Chicago, Illinois.

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# TESTOSTERONE PELLET IMPLANTATION

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TESTOSTERONE has found a definite place in the treatment of certain human diseases and syndromes. Although its value has been widely discussed and debated, it is nevertheless a specific therapy in conditions such as eunuchoidism and hypogonadism. The preparations and modes of administration vary—testosterone in oil by injection, methyl testosterone by mouth or sub-lingually, testosterone in cream byunction, and so on. A previous paper (1) dealt with the implantation of testosterone pellets<sup>1</sup> as a method of administration. At that time a report was made of observations on 130 implants in 47 patients. Since then 52 more pellet implantations have been made, making a total of 182 in 61 patients. As proof of its practicability, efficacy, and desirability, this further report of two selected cases, who have received 19 and 12 implants respectively, is herewith presented.

## Case 1

E W presented himself at the age of 32 years on January 23, 1941. He was a typical eunuch with the classical symptoms and signs. At an early age he had become aware of his hypogonadism (infantile penis, absence of testes, failure of facial hair to appear, scant axillary and supra-pubic hair, etc.). At the age of 26 years he had been treated with pituitary hormone preparations, and, later, with testosterone propionate in doses ranging from 2.5 mg. to 50 mg. at intervals of from two to seven days. The response had encouraged him to continue therapy, but he had frequently neglected treatment. The first implant was made on January 30, 1941 and the dates of the subsequent implants are as follows: no. 2, March 31, 1941, no. 3, August 18, 1941, no. 4, December 24, 1941, no. 5, March 14, 1942, no. 6, June 6, 1942, No. 7, September 8, 1942, no. 8, December 1, 1942, no. 9, February 25, 1943, no. 10, May 24, 1943, no. 11, August 25, 1943, no. 12, November 19, 1943, no. 13, February 11, 1944, no. 14, May 5, 1944, no. 15, July 28, 1944, no. 16, October 23, 1944, no. 17, January 16, 1945, no. 18, April 4, 1945, and no. 19, September 4, 1945. The total is nineteen to date. He now shaves every other day, erections are frequent, the penis has grown to normal adult size and body hair is normal. He has become happy, contented, and masculine, and his only concern is whether the pellets will continue to be available.

## Case 2

D K T first appeared on October 13, 1941, aged 23 years. His complaints were "failure to develop as a male," first recognized at the age of ten years. He was a classical example of eunuchoidism. At the age of eight years and also at 12 years he was circum-

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<sup>1</sup> The testosterone pellets were supplied by the Schering Corporation through Dr. Max Gilbert.

cised, but on presentation his penis measured about 1 cm. About four years ago he had received his first implant on November 1, 1941, and, subsequently, no. 2, on February 7, 1942; no. 3, May 23, 1942; no. 4, September 5, 1942; no. 5, January 26, 1943; no. 6, May 11, 1943; no. 7, September 24, 1943; no. 8, February 1, 1944; no. 9, June 22, 1944; no. 10, November 7, 1944; no. 11, March 27, 1945; and no. 12, August 22, 1945. The total is 12 to date. He has been married since June, 1943. He shaves once a week; erections are frequent; the penis (erect) is 9.2 cm. ( $3\frac{3}{4}$  inches) in length; body, axillary, and suprapubic hair are fair in amount; he cohabitates regularly and satisfactorily, and leads a normal adult life.

### IMPLANTATION METHOD

The first implants were made with the original trocar (1). Since then the new bevel-edged trocar has been used. The posterior axillary area (right or left side) has remained the favorite site. Two to three cubic centimeters of two per cent procaine (with or without epinephrine 1-50,000) is infiltrated under the skin. The trocar is plunged through the skin at an acute angle, the inner plunger withdrawn, and three, 75 mg. pellets are introduced and pushed through with the rod. The trocar is then partially withdrawn and re-inserted at a slight angle and distance from the first three pellets, through the original puncture wound. Again three pellets are introduced. The trocar is then withdrawn, pressure made for a few minutes, to control the oozing or bleeding, which is usually very slight, and a simple dry dressing applied. After five or six days this is removed and invariably the wound is found perfectly healed. After two months the site of implantation is hardly recognizable.

### EFFECTS AND RESULTS

Following regularly repeated implantations a more or less continuous flow of testosterone to the body probably occurred as judged by the reports of the patients. The clinical response has been maintained, both subjectively and objectively. Determinations of 24-hour urine 17-ketosteroids at intervals have consistently shown the amounts excreted in 24 hours to vary from 12.1 mg. to 19.5 mg. The excretion for the two patients reported above was 5.3 mg. and 8.4 mg. before therapy was begun, and varied from 12.8 mg. to 19.1 mg. in the years following the onset of treatment. When re-implantation was made regularly (three to four months), a "decline" or subsidence of testosterone effects did not occur. The metabolic effects of testosterone, such as retention of nitrogen, sodium, water, *etc.*, have been maintained (2).

The dosage is not left to the patient. There is not the possibility of omission of therapy. Frequently repeated injections are made unnecessary. The patient is kept under medical observation and supervision. Occasionally a pellet has been extruded. Infection did not occur. The procedure has been found simple, safe, painless, and satisfactory. The dose has been six,

75 mg. pellets inserted as described. The implantation scars are barely recognizable after a few months. A number of patients, who had tried the various forms of administration, expressed a preference for the implantation method.

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# A CASE OF PRIMARY AMENORRHEA

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THE therapeutic approach to primary amenorrhea due to pituitary or ovarian failure constituted one of the most unyielding problems among gynecologic endocrine disorders until the isolation and synthesis of the female sex hormones made available potent preparations for effective replacement therapy. Since clinical results with hormonal treatment have been described in a limited number of cases only, a report of further experiences along these lines seems warranted. Moreover, the case to be presented seems of particular interest, as uterine bleeding from a secretory endometrium was obtained both by parenteral and by oral therapy. Similar effects recorded in the literature were accomplished in secondary amenorrhea. In primary amenorrhea, Finkler (1) described bleeding from an endometrium "suggestive of a secretory phase" following cyclic hormonal treatment by the parenteral route only.

## CASE REPORT

H. L., aged 22, presented herself with the chief complaint of never having menstruated. Her past history and that of her family were unessential. She was of German-Jewish extraction, the elder of two sisters; the younger sister was normally developed, married, and the mother of a healthy infant. The patient was emotionally undisturbed by her developmental abnormality.

## PHYSICAL EXAMINATION

Patient was younger in appearance than her age, with pleasant feminine features. She was 157 cm. tall, with a high waistline, the lower measurements exceeding the upper ones. The span was 6.5 cm. longer than the height. The body contours showed feminine lines; in spite of general slenderness, there was pronounced obesity of the waistline and hips. The extremities were well shaped and the fingers did not show marked tapering. The breasts were flat cushion-like elevations and the mamillae were not developed; breast tissue was not palpable. There was no pubic hair, but a few axillary hairs were present. (Fig. 1A, 1B). The external genitalia were greatly underdeveloped, the labia minora forming thin folds and the labia majora low elevations. The hymen was intact and delicate. The vagina was short but of normal diameter. Palpation revealed the uterus to be small and in normal position; the vaginal portion was exceedingly small but of typical appearance. The corpus-cervix ratio was of the adult type.

## THERAPY

A diagnosis of hypo-ovarianism with hypogenitalism and primary amenorrhea was made and substitutional therapy instituted. This may be divided into four phases as shown below.

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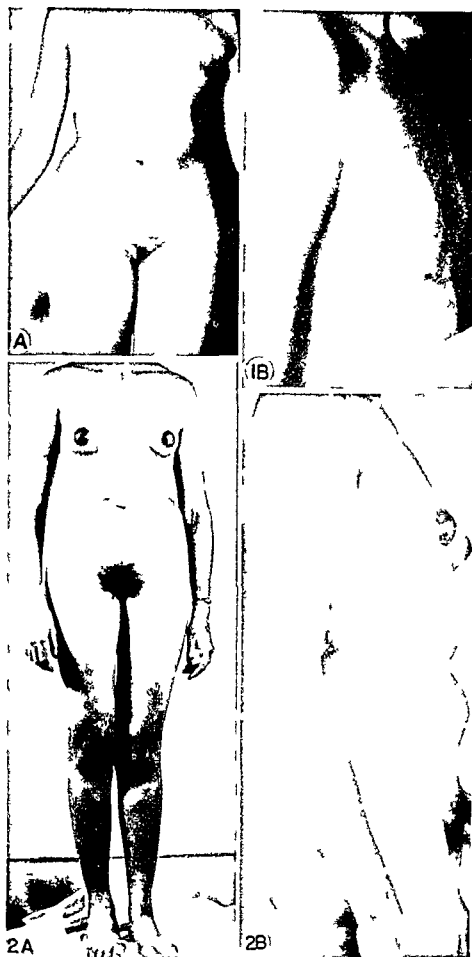


FIG 1A Patient, *H L*, aged 22, photograph showing marked hypogonadism before institution of hormonal therapy

FIG 1B Lateral view of patient *H L* This photograph was taken at the same time as Figure 1A

FIG 2A Anterior view of patient *H L* after six months of hormonal therapy Note development of breasts and of pubic hair

FIG 2B Lateral view of patient, *H L* This photograph was taken at the same time as Figure 2A

**First phase.** The implantation of 72 mg. estrone in two doses given two weeks apart resulted in gradual mammary growth and in the appearance of pubic hair and increase of axillary hair. Yet, no obvious development of the external or internal genitalia oc-

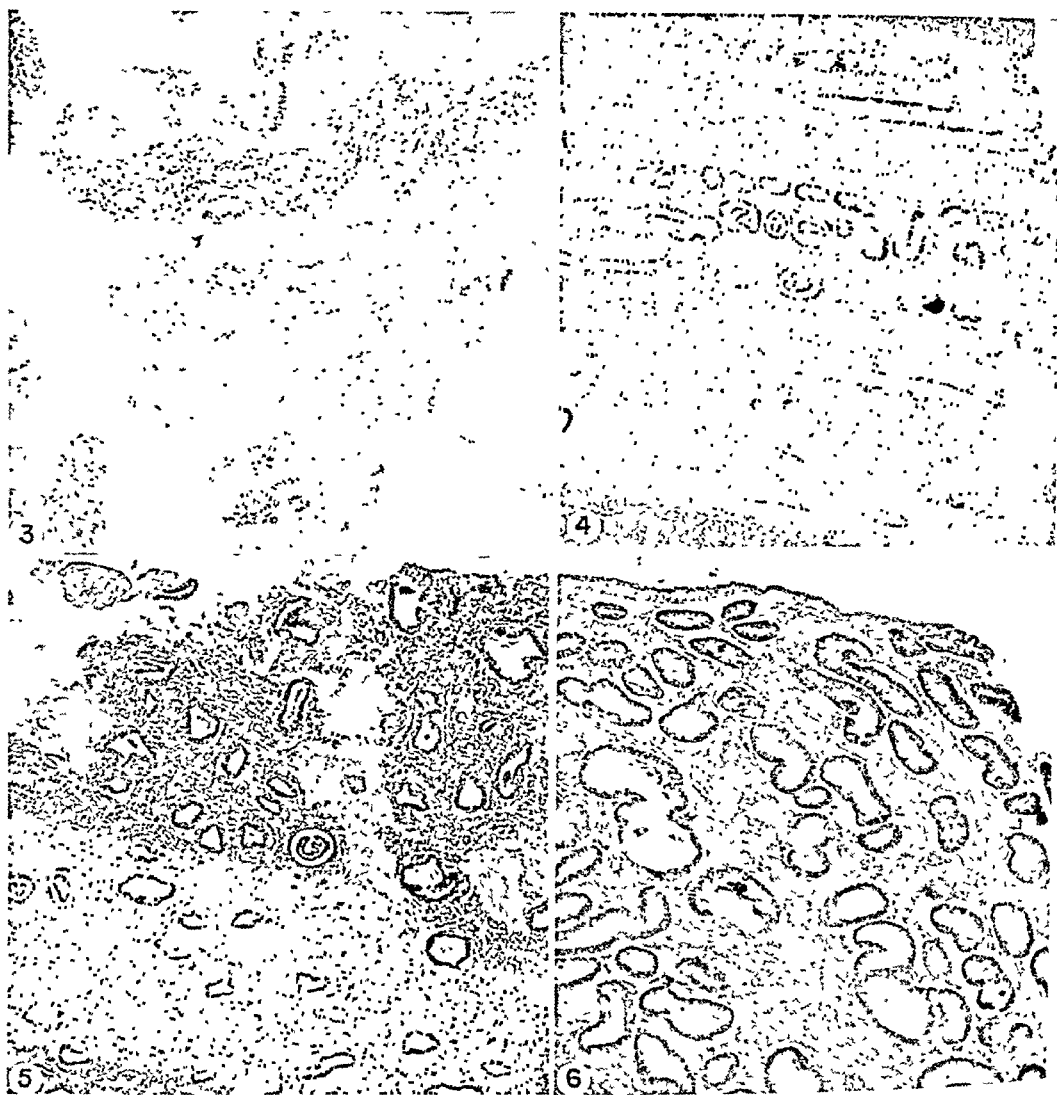


FIG. 3. Biopsy, March 7, 1941. A few epithelial cells in blood; no endometrial mucosa.

FIG. 4. Biopsy, May 24, 1941. Proliferative endometrium following intensive parenteral treatment with estradiol benzoate.

FIG. 5. Biopsy, June 30, 1941. Early secretory endometrium produced by several courses of parenteral cyclic treatment with estradiol benzoate and progesterone.

FIG. 6. Biopsy, November 16, 1941. Secretory endometrium produced by oral replacement therapy with estradiol and pregneninolone.

curred during a period of three months. There were no bleeding episodes, but the emotional life of the patient exhibited marked changes, inasmuch as she began to lead an active dream-life focussed on sexual motives.

The vaginal smear which originally presented a high degree of atrophy showed 30

per cent cornification one month after initiation of therapy followed by a gradual return to the pretreatment status. Biopsies were attempted four weeks and three months after the first implantation, but in neither case could endometrial tissue be obtained (Fig. 3).

**Second phase.** The implants having been completely absorbed during the preceding three months, the patient was given five courses of cyclic intramuscular injections of estradiol benzoate and progesterone within four and one-half months. It was intended to follow in general a dosage plan consisting of a total of 50,000 R.U. of estrogenic hormone during the first half, and of a total of 50 mg. of corpus luteum hormone combined with some estrogenic medication during the second half of the hypothetic cycle. However, certain deviations from this plan became advisable when bleeding occurred before termination of a given course of therapy and, furthermore, when the large doses of estrogens administered had brought about such marked developmental changes as to give the patient in every respect the appearance of a normally built mature woman (Fig. 2A, 2B).

Every such course of therapy induced bleeding lasting from three to five days. Repeated biopsy studies, at the end of the estrogenic phases of treatment, always revealed active proliferation. Fig. 4 shows the endometrial pattern of a specimen obtained during the third course of treatment when patient was transferred from estrogenic to progestogenic therapy. Early secretory activity (Fig. 5) was apparent in the specimen obtained at the end of the fourth course of treatment, following administration of a total of 50 mg. of progesterone in five divided doses over a period of one week. However, at the end of another full course of cyclic therapy the endometrium did not reveal progestational changes. Interruption of hormone administration for several weeks was accompanied by return of an atrophic endometrium.

**Third phase.** In order to determine whether oral medication also would elicit bleeding from a secretory endometrium a state of hormonal depletion was induced by withholding treatment for six weeks and by then instituting oral therapy. This consisted of five courses of cyclic treatment with estradiol and pregnenolone over a period of 14 months. The total amounts of estradiol administered during the first phases of the hypothetic cycles were 24, 48, 10, 10, and 10 mg. spread over 12, 12, 5, 10, and 10 days respectively. After such priming, the progestogenic hormone was given either alone or in combination with estradiol. The total amounts of pregnenolone were 500, 1000, 350, 420, and 750 mg. spread over 10, 10, 5, 6, and 5 days respectively. There was uterine bleeding four times during these five courses of oral therapy. Secretory activity of the endometrium (Fig. 6) resulted after the patient had received 1000 mg. of pregnenolone (second course of treatment). Similar results were obtained following 750 mg. of pregnenolone (fifth course of treatment), but no progestational changes occurred following smaller doses. Seemingly it matters little whether the amount of pregnenolone required is spread over 5 or 10 days. Table 1 gives the details of these three phases of treatment.

**Fourth phase.** During the following years therapy was of necessity irregular, and was dependent upon the free hormone supplies available for the indigent patient. During this period the results as evidenced by endometrial biopsies reflected exactly the amounts and types of hormones administered. In general a lower dosage was required for maintenance therapy than for stimulation of developmental changes.

The patient, now 27 years of age, reports sporadically to the clinic. She is able to maintain physical and mental equilibrium by periodical intake of various artificial estrogenic preparations. Female characteristics remain well developed; bleeding occurs from two to three times a year and she has become reconciled to a physical deficiency which, however, is no longer readily apparent.

TABLE 1

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
First Phase				
12/14/40	Implant: 20 mg. estrone crystals			
12/21/40	Implant: 52 mg. estrone pellets			
1/18/41				No tissue obtained.
3/7/41				No tissue obtained.
Second Phase				
3/17/41	1.67 mg. E.B.			
3/19/41	1.67 mg. E.B.			
3/21/41	1.67 mg. E.B.			
3/24/41	1.67 mg. E.B.			
3/31/41	1.67 mg. E.B.			
4/2/41		10 mg. P.		
4/5/41	1.67 mg. E.B.	10 mg. P.		Active proliferation.
4/7/41		10 mg. P.		
4/9/41		10 mg. P.		
4/11/41		10 mg. P.	Bleeding 5 days.	
4/22/41	1.67 mg. E.B.			
4/26/41	1.67 mg. E.B.			
4/28/41	1.67 mg. E.B.			
4/30/41	1.67 mg. E.B.			
5/3/41	1.67 mg. E.B.			
5/5/41	1.67 mg. E.B.			
5/6/41				Full proliferation.
5/7/41		10 mg. P.		
5/9/41			Bleeding.	
5/10/41		10 mg. P.		
5/12/41	1 mg. E.B.			
5/14/41	1 mg. E.B.			
5/17/41	1 mg. E.B.			
5/19/41	1 mg. E.B.			
5/21/41	1 mg. E.B.			
5/23/41	0.33 mg. E.B.			
5/24/41		10 mg. P.		Excellent proliferation.
5/26/41		10 mg. P.	Spotting.	
5/28/41	1 mg. E.B.	10 mg. P.	Bleeding several days.	
5/29/41	1 mg. E.B.	10 mg. P.		
6/13/41				Atrophy.
6/14/41	1 mg. E.B.			
6/16/41	1 mg. E.B.			
6/18/41	1 mg. E.B.			
6/20/41	1 mg. E.B.			

TABLE I (Cont'd.)

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
<b>Second Phase (cont'd)</b>				
6/24/41		10 mg. P.	Bleeding few hours.	Proliferation.
6/25/41		10 mg. P.		
6/26/41		10 mg. P.		
6/28/41	0.33 mg. E.B.	10 mg. P.		
6/30/41		10 mg. P.		
7/1/41			Bleeding 5 days.	Early secretion.
7/7/41	0.33 mg. E.B.			
7/11/41	0.33 mg. E.B.			
7/14/41	0.33 mg. E.B.	10 mg. P.		
7/19/41	0.33 mg. E.B.	10 mg. P.		Proliferation.
7/21/41		20 mg. P.		
7/24/41	0.33 mg. E.B.	10 mg. P.		
7/26/41		10 mg. P.		No secretion.
7/30/41			Bleeding 3 days.	
<b>Third Phase</b>				
9/11/41 to	2 mg. E. daily			Atrophy (9/11/41)
9/22/41				Proliferation (9/22/41)
9/23/41 to		50 mg. Po. daily	Bleeding 6 days.	
10/2/41				
10/8/41				Hypoplasia.
10/26/41 to	4 mg. E. daily			
11/6/41				
11/7/41 to	0.4 mg. E. daily	100 mg. Po. daily	Bleeding.	Secretion (11/16/41)
11/16/41				
6/15/42	0.33 mg. E.B.			
6/17/42	0.33 mg. E.B.			
6/19/42	0.33 mg. E.B.			
6/22/42	0.33 mg. E.B.			
6/24/42	0.33 mg. E.B.			
6/26/42	0.33 mg. E.B.			
6/29/42		10 mg. P.		
6/30/42		10 mg. P.		
7/1/42		10 mg. P.		
7/3/42		10 mg. P.		
7/6/42				Secretion.
7/7/42			Bleeding 5 days.	

TABLE I (Cont'd.)

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
<b>Third Phase (cont'd)</b>				
8/25/42 to 8/29/42 8/30/42 to 9/3/42 9/4/42	2 mg. E. daily			
9/26/42 to 10/5/42		70 mg. Po. daily		
10/6/42 to 10/11/42	0.4 mg. E.	70 mg. Po.	Staining 5 days.	Atrophy. Hyperproliferation.
10/21/42 to 10/30/42	1 mg. E.			
10/31/42 to 11/4/42	0.4 mg. E.	150 mg. Po.		Atrophic endometrium.
11/6/42			Bleeding 3 days.	Secretory endometrium.

## KEY:

E.B. = Estradiol Benzoate

E. = Estradiol

P. = Progesterone

Po. = Pregneninolone

Schedule of treatment of patient H. L. during a 2-year period. Endometrial response to therapy and bleeding episodes.

## DISCUSSION

Other workers have found pituitary gonadotrophic substances of no avail in inducing normal ovarian function in patients with primary amenorrhea. However, there are on record cases in which feminization including bleeding from a secretory endometrium was attained by cyclic replacement therapy consisting of the parenteral administration of gonadal hormones.

In the case presented, exhibiting extreme hypogenitalism and primary amenorrhea, implantation of 72 mg. of estrone initiated the development of secondary sex characteristics but was ineffectual in developing the endometrium and in producing uterine bleeding. However, cyclic therapy with estrogenic and progestogenic hormones administered parenterally or orally

caused proliferation and secretory changes in the endometrial mucosa indistinguishable from those elicited by the hormonal stimuli of normally functioning ovaries. Bleeding occurred repeatedly but could be produced from a progestational endometrium only if the optimal quantitative estrogen-progesterone relation had been established. If oral medication was applied, a minimum of from 750 to 1000 mg. of pregnenolone was required to obtain secretory activity after adequate priming with estradiol. Other investigators had demonstrated that similar quantities of pregnenolone were needed to produce comparable results in surgical castrates and postmenopausal women. For instance, Neustaedter (2) demonstrated that from 900 to 1200 mg. of pregnenolone caused secretory changes in the endometria of six surgical castrates. Binberg and his group (4) showed that from 1000 to 1200 mg. pregnenolone brought about progestational endometria in four out of six postmenopausal women. In a previous communication (3) the author demonstrated that secretory activity was restored in a case of anovulatory bleeding by two courses of pregnenolone therapy, each of 1000 mg. Thus it seems that if the ovaries are absent or non-functioning, from 750 to 1200 mg. of the orally active corpus luteum preparation will produce endometrial changes identical with those occurring in women of the reproductive age group during the second half of the cycle.

The foregoing case history illustrates what may be expected from oral estrogenic and progestogenic therapy in patients of a similar type.

The estradiol (*Dimenformon*), estradiol benzoate (*Dimenformon Benzoate*), progesterone (*Progestin*), and pregnenolone (*Progestoral*) used in this study were supplied by Roche-Organon, Inc., Nutley, New Jersey, by the courtesy of Dr. Leo A. Park.

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# THE XENOPUS TEST IN TUMOUR OF THE TESTIS

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AND

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**Z**ONDEK, in 1929, employing immature female mice as in the diagnosis of pregnancy, first demonstrated the presence of gonadotrophic hormone in the urine of a man suffering from a teratoma of the testis. In 1930 Heidrich, Fels and Mathias (3) reported a similar observation in a case of chorionepithelioma of the testis. In this case the excretion of the hormone exceeded the remarkable figure of 50,000 "mouse units" per litre of urine. Ferguson (2) advocated bio-assay of the urine for gonadotrophic hormone not only as an aid to diagnosis, but as a guide to the prognosis and radiosensitivity of testicular tumours.

In 1933 Shapiro and Zwarenstein (9) described a test for pregnancy using the South African clawed frog, *Xenopus laevis*. Zwarenstein and Duncan (12), reviewing ten years' experience of the test, described a dilution test for the rough quantitative estimation of gonadotrophic hormone in those cases where the amount excreted was unduly large. The dilution test has proved of considerable value in the diagnosis of hydatidiform mole and chorionepithelioma in the female.

The Zenopus test has also been employed in the investigation of cases of suspected testicular tumours. Some of these proved on histological examination to be chronic inflammatory affections of the testis or epididymis, and in these the test was consistently negative. The remainder, with one exception where there was no histological control and which gave a negative test, are briefly compared in the following table:

Case	Age	Clinical diagnosis	Xenopus test	Histological diagnosis
1	41	Testicular tumour	Negative	Seminoma
2	34	Hydrocele Readmitted after 3 months; ?secondary deposits; clinical examination negative.	Not done	Embryonal adenocarcinoma
3	41	?Testicular tumour  Re-admitted after 2 years; secondary deposits in para-aortic glands.	Positive Negative on neat urine Positive	No autopsy obtained. Teratoma containing a mixture of tissues Chorionepithelioma

4	29	?Testicular tumour	Negative	Seminoma
5	37	Hydrocele + underlying pathology of testis or epididymis	Negative	Embryonal adenocarcinoma
6	50	Testicular tumour	Negative	Melanoma (Secondary deposit)

Cases 2 and 3, in which positive *Xenopus* tests were obtained, are worth recording in some detail.

*Case 2: A. v. W.*, a coloured, male, printer's assistant, aged 34 years, was admitted to the hospital in May, 1936, for "hydrocele." A left orchidectomy was performed, and he was discharged apparently well three weeks later. No *Xenopus* test was performed during this admission. The histological features of the specimen removed at operation were those of a very cellular tumour of the testis, the cells being much less uniform in type than in the common seminoma, and in parts tending to form imperfect acini *i.e.* an embryonal adenocarcinoma.

The patient was re-admitted three months after his discharge, complaining of pain in the left loin and left iliac fossa for seven weeks. His general condition was described as good, and there was no clinical evidence of a local recurrence or of glandular or visceral metastases. The *Xenopus* test, however, was positive.

The patient left the hospital and was confined to his bed until his death five months later. During the latter half of this period he developed paralysis of the lower half of his body. No autopsy was obtained.

*Case 3: A.S.*, a European, aged 43, was admitted to the hospital in November 1942 complaining of swelling of the right testis for seven months and tenderness of the nipples for three months. Orchidectomy was performed for a suspected tumour of the right testis. A *Xenopus* test done on neat urine at this time was negative. No further specimen was submitted for examination, and the patient was discharged apparently fit. The histological appearance of the tumour removed was that of a teratoma showing differentiation into cartilage, muscle, glandular acini, squamous epithelium and myxomatous tissue. In addition there were small, more cellular areas of epithelial tissue, suggesting more active growth.

Two years later the patient returned to hospital complaining of pain in the back and tender swelling of the breasts. Examination revealed gynaecomastia and a hard mass in the epigastrium, presumably metastases in the para-aortic lymph glands. Accordingly he was given a course of deep x-ray therapy to the epigastrium.

Six weeks later he was admitted for excision of the left testis, a procedure prompted by the favourable results following castration reported by Saleeby (8). It was found that the epigastric mass was no longer palpable, and the patient appeared thin but subjectively well. Gynaecomastia was, however, still present and the urine gave a positive *Xenopus* test. The dilution test was negative.

After his discharge from the hospital the patient's condition rapidly deteriorated. Further *Xenopus* tests were positive but the dilution test remained negative. He complained particularly of a sick feeling in the epigastrium, and despite further x-ray therapy, became emaciated, cachectic, and died in February, 1945.

At post-mortem the liver was found greatly enlarged (3300 gm.), and contained numerous deposits of reddish-yellow tumour tissue. The abdominal lymphatic glands were extensively invaded, and metastases were found also in the lungs, pancreas and adrenal glands. The adrenals were completely destroyed and replaced by tumour tissue. A portion of this was ground up with sand, and the extract obtained was injected into

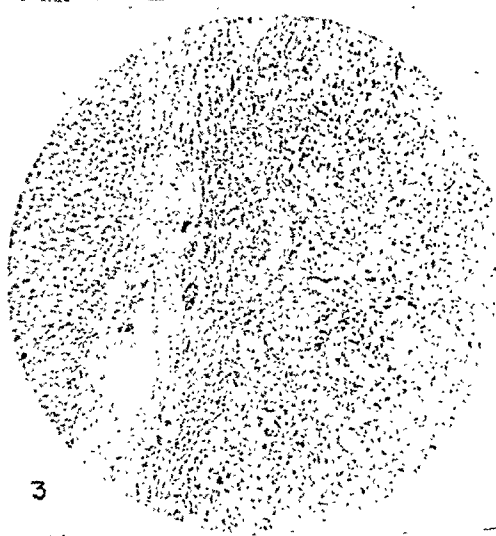
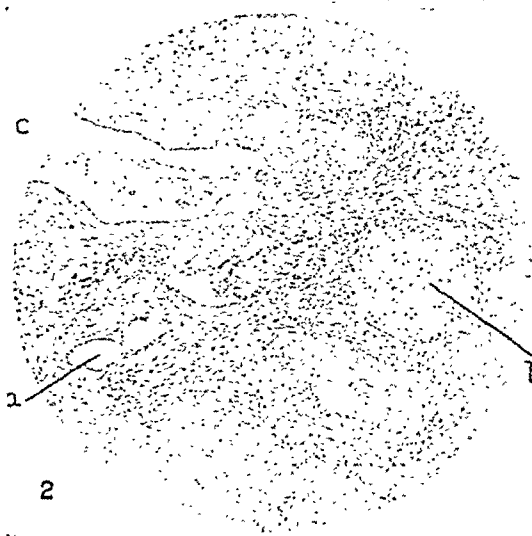


FIG. 1: Section of embryonal adenocarcinoma ( $\times 100$ ). The cells vary much in appearance and show a tendency to be grouped in acini as at (a) and (b).

FIG. 2: Section of teratoma containing a mixture of tissues ( $\times 100$ ): (a) gland acini, (b) cartilage, (c) cyst lined by flattened epithelium.

FIG. 3. Microphotograph showing invasion of liver tissue by chorionepithelioma ( $\times 100$ ).

frogs as in the routine pregnancy test. Ovulation occurred, indicating the presence of a gonadotrophic substance. A control test with normal adrenal tissue gave a negative result.

Histological examination of the organs removed at autopsy showed very extensive invasion by tumour tissue, the structure being that of a chorionepithelioma.

The breasts showed typical gynaecomastia.

## DISCUSSION

Using the "mouse test," Zondek (11) found that while the luteinizing reaction (dependent on chorionic gonadotrophin) occurred in relatively few (three out of 14) cases of testicular tumour, a follicle-stimulating reaction was obtained much more frequently, and could occur even in non-neoplastic disease of the testis. Here it was apparently due to overaction of the pituitary consequent in the destruction of one testis.

Ferguson (2) maintained that the hormone output of testicular tumours could be closely correlated with their histological structure, so that a fairly accurate diagnosis could be made from a bio-assay of the urine. The hormone content was highest in chorionepithelioma, lowest in the "adult" mixed teratoma, while embryonal carcinoma and seminoma occupied intermediary positions. He recorded his results in units of "Prolan A" without differentiating between follicle-stimulating and luteinizing hormone.

Others, however, believed such a distinction to be of value, and Montpellier and Herland in 1933, and Seror in 1935 [quoted by McDonald (6)], were of the opinion that a seminoma could be differentiated from a chorionepithelioma by means of the Aschheim-Zondek reaction. Urine from a case of chorionepithelioma contained chorionic gonadotrophin and gave the complete reaction with the formation of corpora lutea, while with seminoma only follicular maturation occurred.

Hamburger [quoted by Twombly *et al.* (10)] went further and considered that chorionic gonadotrophin occurred in the urine of patients with chorionepithelioma and adenocarcinoma, while in cases of seminoma (including embryonal carcinoma with or without lymphoid stroma) follicle-stimulating hormone only was found.

The belief that chorionic gonadotrophin is not found exclusively in cases of chorionepithelioma is supported by Twombly *et al.* (10). These authors, however, disagree with Hamburger and contend that both types of gonadotrophic hormone are found in each group of patients. Occasionally they occur together but one usually predominates. From an analysis of a large number of cases these authors conclude that there is little correlation between the histological structure of testicular tumours and the type and quantity of hormone excreted in the urine, so that the histology of a tumour is not predictable from bio-assay of the urine alone.

In the face of such conflicting opinion it becomes difficult to assess the actual diagnostic value of bio-assay of urine in cases of suspected testicular tumour. Perhaps the confusion is in part due to the use, as test animals, of unhypophysectomised mice and rats, as Noble *et al.* (7) have shown that the test animal's own pituitary may considerably modify the effects of injected gonadotrophic substances. The difficulty is circumvented by the

use of *Xenopus laevis* for the test. In this animal the presence of ovulation constitutes a positive result. Ovulation will occur if the extract of urine injected contains sufficient chorionic gonadotrophin, but if it contains only follicle-stimulating hormone the test will be negative.

Hitherto, only two cases of testicular tumour have shown a positive *Xenopus* test. In one of these (*Case 3*) there was a widely disseminated chorionepithelioma, but in *Case 2* the nature of the tumour at the time of the test was not known. The primary growth in *Case 2* was an embryonal adenocarcinoma but no test was done until three months after its removal. The positive result then obtained was the first definite indication of the presence of metastases. Unfortunately their histological structure was never ascertained as there was no autopsy.

The *Xenopus* test has, therefore, not yet shown whether chorionic gonadotrophin may occur in the urine of cases of testicular tumour other than chorionepithelioma. Pending further experience it may be concluded that the test is of rather limited diagnostic value, but inasmuch as it may disclose the presence of chorionic tissue it should form part of the investigation of all cases of suspected testicular neoplasm, and may be of considerable value in the early detection of secondary or metastatic tumour growth after orchidectomy.

### Prognosis and radiosensitivity

Ferguson (2) found that in the majority of his cases there was a reduction in the excretion of gonadotrophic hormone in the urine after irradiation of the primary tumour or its metastases. Thus, he considered that repeated bio-assay of the urine supplied a good index of the radiosensitivity of tumours of the testis, and hence a valuable guide to prognosis.

Subsequent work has, however, only partly supported this view. In some cases [Beilly *et. al.* (1)] it has been possible fairly accurately to follow the clinical course by repeated quantitative estimation of the gonadotrophic hormone excreted in the urine. More often, however, the results have been disappointing. Hinman and Powell (4) concluded that such failure might be due to the likelihood of x-ray therapy inhibiting the ability of a tumour to produce gonadotrophic hormone without destroying the tumour. In one of our cases, *No. 3*, this might explain why, despite x-ray therapy, the malignant disease progressed to a fatal issue without there occurring a rise in hormone output sufficient to give a positive dilution test.

In a later publication, Hinman and Powell (5) expressed their conviction that while quantitative estimations of hormone output alone were unreliable indications of prognosis after irradiation, very helpful information

could be obtained by correlating the hormone output of a tumour with its histological structure, and grading it according to a hormonal-histological classification. This procedure, in then cases, proved of great value in determining prognosis and treatment.

Twombly *et al.* (10) (1942) are of the opinion that repeated hormonal tests are of little value in following the clinical course, and in most cases are not worth doing. They believe, however, that the test should be performed on all cases in order to determine whether the tumour is producing chorionic gonadotrophin, as this is a bad prognostic sign. They attach little prognostic significance to the presence in the urine of follicle-stimulating hormone.

In this respect the *Xenopus* test would be of considerable value. Unfortunately it has, as yet, found very limited application in the diagnosis and study of neoplasms of the testis. The results obtained, however, have conformed well with what could be expected on theoretical grounds, and it is hoped that it will more often be resorted to in the future.

#### SUMMARY

The *Xenopus* test has been performed in a series of cases of suspected testicular tumour, and a positive result was obtained in two of these.

The diagnostic and prognostic value of bio-assay of the urine in cases of tumour of the testis is discussed. It would seem that it is particularly desirable to ascertain whether or not chorionic gonadotrophin is being excreted, and for this purpose *Xenopus laevis* is an eminently suitable test animal.

#### ACKNOWLEDGEMENTS

We are indebted to Professor B. J. Ryrie for placing at our disposal the histological material of the Department of Pathology and to Mr. I. de Villiers for the preparation of the microphotographs.

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## Book Review

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SHERF, DAVID and T. J. BOYD. *Clinical Electrocardiography*. Philadelphia, Pa., J. B. Lippincott Company, 1946, 267 pp., 2nd ed.

The book reviewed is an American edition, while two previous editions were published in England. There were editions in French, Spanish and Portuguese.

This book has many features which distinguish it from other textbooks on the subject. One is the fact that the authors are not dogmatic and do not assume the rôle of authoritative finality. This is a very healthy attitude toward electrocardiography. This is not merely a collection of tracings with explanatory remarks, but actually a text with illustrations. The many pitfalls and problems facing the present state of electrocardiography are discussed especially well in the chapters on "Bundle Branch Block" and "Chest Leads." Another useful feature of the book is the extensive list of references attached to each chapter; the space devoted to references in some chapters is greater than the text on the subject itself. The book is thus useful as a ready reference index for the student of the subject.

While the book is published neatly, the material is not always arranged in a palatable form. There is, for instance, a special chapter on the deep Q3. The significance of this abnormality, however, is discussed separately in the chapter on coronary thrombosis.

On the whole it is a very useful book to read and study after one has attained an elementary knowledge of the subject from the leading textbooks on cardiology.—L.S.





## Abstracts of

# CURRENT ENDOCRINE LITERATURE

*Editor*; D. A. MCGINTY. *Collaborators*: A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN JR., G. G. RUDOLPH, L. T. SAMUELS.

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## GONADS

BADENOCH, A. W. Descent of the testis in relation to temperature. *Brit. M. J.* 2: 601-603 (1945).

The author has studied the intrascrotal and peritoneal temperatures in twenty-five adults at the time of operation for inguinal hernia. The temperature was invariably lower in the scrotum than in the iliac fossa. The difference varied from 0.8° C. to 3.7° C. with an average difference of 2.2° C. The influence of temperature on spermatogenesis was reviewed.—*L.T.S.*

BURDICK, H. O. Further observations on induced ovulation in the mouse as a rapid test for pregnancy. *Am. J. Physiol.* 145 (3): 387-390 (1946).

Mature albino mice of the Rockland strain weighing at least 20 gm. and having vaginal smears showing an abundance of leucocytes typical of diestrus were used as the basic test animal. Samples of morning urine were refrigerated without preservative. Single subcutaneous injections of untreated urine were made and autopsies performed 18 to 24 hours later. Ovulation is manifest by the distention of the ampulla of the oviduct with fluid and the egg mass, and can be seen with a dissecting microscope. The occurrence of ovulation is regarded as a definite end point of the test. The chorionic gonadotropin content of urines from pregnancies of six to eight weeks' duration contained from 10,000 to 80,000 mouse ovulating units per liter. The minimal ovulating doses of urine containing 10,000 mouse ovulating units per liter is 0.1 cc. There was usually a marked reduction in ovulating capacity by the third month of pregnancy. The potency of stored urine was maintained for approximately 30 days. It was found that pregnant mice could be used as test animals provided they were not injected within the first three days of pregnancy while the fertilized ova were still in the oviducts. Pregnant mice were slightly more responsive than diestrus mice.—*F.N.A.*

CALATRONI, C. J., V. RUIZ, AND G. DI PAOLA. Castration during pregnancy. *Obst. y ginec. latino-am.* 3: 145 (1945).

Fraenkel observed in rabbits that castration during pregnancy caused miscarriage.

The authors have examined the literature and analyzed the results in a series of 85 women who were surgically castrated during the first four months of pregnancy in order to determine whether miscarriage follows castration during pregnancy in women. The series included only patients to whom no morphine, progesterone or any other abortion-preventing medication had been given after the operation. Cases in whom only the corpus luteum or the ovary containing it was removed were not included in the analysis. Of the 85 cases studied, five were operated on during the first month of pregnancy, 29 during the second month, 27 during the third month, 20 during the fourth month, and four at an unspecified time during the first four months. Of these 85 cases, 65 (76.4 per cent) had a normal delivery, 13 (15.2 per cent) miscarried, 6 (7 per cent) were still pregnant at the time of the survey, and 1 (1.1 per cent) was delivered about 15 days before term. A study of the patients that miscarried showed that in three cases the mothers died three hours, 12 and 15 days, respectively, after the castrating operation, one of them with neoplastic metastases. The authors conclude that these three cases aborted because of the conditions which lead to their deaths rather than from the castration. Another case that presented symptoms of abortion was operated upon, and hence was excluded from the group. Hence, the number of miscarriages attributed to the loss of the corpus luteum is reduced to nine (10.5 per cent), a rate of miscarriage similar to that observed after any abdominal operation in pregnant women. The authors conclude that once the ovum is lodged in the uterus it does not need the corpus luteum, and hence excision of ovarian tumors during pregnancy should not be feared. The paper contains 127 references and five tables.—*J.R.R.-M.*

DAUGHTRY, D. C. Arrhenoblastoma. *Am. J. Obst. & Gynec.* 50 (5): 539-541 (1945).

The author reported an instance of arrhenoblastoma in a 37 year old, married, nulliparous colored woman. Six months following surgical removal there was a marked decrease in masculine features.—*C.D.D.*

DAVIS, C. D. AND E. C. HAMBLIN. A comparative study of the clinical responses of women with hypofunctioning ovaries to two methods of combined gonadotropic therapy. *Am. J. Obst. & Gynec.* 50 (3): 269-274 (1945).

Twenty-one patients with degrees of hypo-ovarianism varying from deficient sexual maturation to presumed ovarian sterility associated with bleeding from immature gestational endometrium, were subjected to two systems of gonadotropic therapy. The primary criterion for evaluation of the responses was a study of endometrial biopsies taken prior to and following treatment.

One method of therapy employed the single and sequential administration of equine and chorionic gonadotropins; the so-called one-two cycle gonadotropic therapy. The other method of therapy employed a preparation which contained a mixture of 'pituitary synergist' and chorionic gonadotropin, which had to be given daily from the fifth through the twenty-fourth days of the cycle in order to produce any positive responses.

The authors concluded that both types of therapy were effective in producing gestational endometriums in patients experiencing various grades of estrogenic bleeding but that the latter type of therapy yields a lower incidence of positive responses and a higher incidence of untoward reactions.—*C.D.D.*

EREZ, NASID. A case of Meig's syndrome. *J. Obst. & Gynaec Brit. Emp.* 52 (5): 506-509 (1945).

A case of Meig's syndrome reported from Istanbul showed ascites, right pleural effusion and a fibroma of the right ovary, the size of a foetal head. Recovery followed removal of the tumor. This is said to be the 42nd recorded case.—*R.A.C.*

EVERIDGE, J. Case of pseudohermaphroditism and adrenalism. *Proc. Roy. Soc. Med.* 38: 649 (1945).

The author reports a case of a 19-year-old patient whose sex could not be determined at birth. The individual was born with two teeth and walked and talked at nine months. Axillary and pubic hair appeared at the age of three years. Shaving was begun at nine and the voice changed at 12. At ten there was periodic abdominal pain and monthly discharge of blood from the urethra. From the age of 11 there was periodic swelling of the breasts. The patient was unusually bright, preferred masculine pursuits, and was a good athlete. There was no evidence of a sexual psychological problem. The 17-ketosteroids in urine were 75.7 mg. per 24 hours. Laparotomy revealed female genital organs and the uterus and one ovary were removed. There was no enlargement of the adrenals. The vagina opened into the urethra. No postoperative values on ketosteroids were given, and no description of the ultimate development of the external genitalia.—*R.C.*

FAULKNER, R. L. AND E. A. RIEMENSCHNEIDER. Reactivation of endometriosis by stilbestrol therapy. *Am. J. Obst. & Gynec.* 50 (5): 560-561 (1945).

The authors reported a patient with severe periodic bleeding from endometriosis of the bowel which required in all over seventy partial or whole transfusions. Surgical castration was finally done and the patient had no more bleeding until given diethylstilbestrol for menopausal symptoms. This led to a severe recurrence of bleeding. Permanent recovery followed discontinuance of this therapy.—*C.D.D.*

FRANK, I. L. Uterine bleeding and extragenital disturbances. *Am. J. M. Sc.* 210: 787 (1945).

In this review article the author analyzes 125 communications from the literature in terms of extragenital disturbances and diseases of the body that have been reported to be associated with uterine bleeding in order to estimate the frequency and importance of such causes. He discusses: 1) the influence of the central nervous system, 2) physical agents, 3) diseases of the endocrine glands, 4) infectious diseases, 5) allergy and the menstrual cycle, 6) blood dyscrasias, 7) avitaminosis, 8) visceral disease, and 9) atypical bleeding of physiologic origin. He concludes that the ultimate origin of very many cases of dysfunctional uterine bleeding is not sought out, because physicians have been willing to accept as causes either minor incidental pelvic lesions or endocrine imbalances, which may be merely intermediate effects. Relief following hormone therapy or curettage does not demonstrate a primary disease, and both may be followed by a recurrence of menorrhagia. Uterine bleeding has two dangerous implications: cancer and blood loss. The latter usually receives prompt therapy, but the former is insidious and cannot safely be kept waiting. Metrorrhagia usually means a neoplastic lesion of the uterine epithelium and demands an early diagnostic curettage. Menorrhagia, however, is almost always

benign. Tracing menorrhagia to an otherwise subclinical disturbance is a tedious and uncertain process, but on occasion it will suggest cures rather than palliatives, and may often avert unnecessary or fruitless surgical procedures. Accumulating data indicate that uterine bleeding commonly derives from systemic rather than purely local disturbances.—*E.C.R., Jr.*

GILL, A. J., G. T. CALDWELL, AND J. L. GOFORTH. Choriocarcinoma of the testicle. *Am. J. M. Sc.* 210: 745 (1945).

The authors report the history and pathological findings of three recent cases of choriocarcinoma of the testicle. After histological study of these cases and consideration of part of the extensive literature on the subject, they believe that these tumors arise from primitive cells which have essentially the same capacity as the developing ovum and that the malignant trophoblastic elements of these tumors are derived from ectoderm in the same way as the comparable tissue in ordinary pregnancy. They consider that the cells from which these tumors arise are multipotential sex cells normally present in the adult testicle; these cells are probably spermatogonia. The authors think that the differentiated elements of the teratoma in testicular tumors are probably not responsible for any hormone production which may be observed, and that it is unlikely that any of the testicular tumors with the exception of the choriocarcinoma elaborate any hormone of themselves. They believe that the finding of gonadotrophic hormones in these other tumors suggests either undisclosed trophoblastic tissue or a systemic endocrine dysfunction which, as others have pointed out, may have preceded the occurrence of the tumor.—*E.C.R., Jr.*

GREENE, R. D. B. E., A new synthetic estrogen. *Brit. M. J.* 1: 9-10 (1945).

The synthetic pro-estrogen alpha, alpha-di-(p-ethoxyphenyl)-beta-phenylbromomethyl-ene was administered to patients suffering with mild menopausal symptoms, to three cases with carcinoma of the prostate and three patients with uterine atrophy. In the six patients with vasomotor symptoms of the climacteric the drug given orally in doses of one to two grams brought relief from symptoms for two to three weeks. The good effects were maintained by weekly doses of 100 to 300 mg. The three cases of uterine atrophy showed little benefit but did not respond readily to other estrogens. It failed in carcinoma of the prostate; two patients who showed no improvement with D. B. E. responded dramatically to stilbestrol. The drug seems to be inferior to other synthetic estrogens in some respects and its only advantage is a prolonged action which allows weekly doses to be used.—*L.T.S.*

HUGGETT, A. ST. G. AND J. J. PRITCHARD. Experimental fetal death: the surviving placenta. *Proc. Roy. Soc. Med.* 38: 261 (1945).

The placental structure in rats was studied following fetal death produced by 1) crushing the embryos, 2) injection of pregnant mare's serum before the 12th day, 3) injection of estrone on the 9th day, 4) double ovariectomy a) on days seven to ten, b) on the 11th day and c) after the 12th day. Prior to days 11 and 12 estrone, pregnant mare's serum and bilateral ovariectomy caused decidual necrosis and death of the embryos, probably due to an alteration of the estrone/progesterone balance. Placentae survived after fetal death if the mesodermal-allantoic elements were differentiated.—*R.C.*

JONES, G. E. S. AND R. W. TELINDE. The curability of granulosa-cell tumors. *Am. J. Obst. & Gynec.* 50 (6): 691-700 (1945).

The authors report three patients who developed recurrences of granulosa-cell tumor not less than 14 years after the original operation. All three have died, at 18, 20 and 21 years respectively, following the removal of the primary tumor in spite of the fact that the tumor originally gave no evidence of malignancy. All three were postmenopausal at the time of their recurrences and all showed clinical signs of estrogenic activity. Total urinary estrogen values were not extremely high in the two of them, falling within the range of values for normal cyclic women.—C.D.D.

KAPLAN, I. I. The effect of radiation on the function of the ovary in young girls: Supplementary report. *Am. J. Obst. & Gynec.* 50 (3): 340-341 (1945).

In 1939, the author reported a patient who at the age of 4½ years received intensive irradiation, x-ray and radium, for a pelvic tumor and who, in spite of this, subsequently had a normal menarche at 12. She continued to menstruate regularly until the age of 19. In 1943, this patient developed metastasis in the region of the coccyx and died a little more than one year later. The pathologic diagnosis was spindle-cell sarcoma, neurogenic type.—C.D.D.

McINTOSH, C. B. AND W. E. BROWN. Adrenogenital pseudohermaphroditism treated with stilbestrol. *J. Pediat.* 27: 322 (1945).

The case is reported of a five-year-old child with the following features: 1) abnormally rapid growth rate with measurements equivalent to average for 7.5 years; 2) uncertain sex, although reared by parents as a girl; 3) physical examination essentially normal except for large size, tendency toward masculine physique, large amount of pubic hair of female pattern, a phallus 2.5 inches in length with a definite glans and prepuce but no urethral opening, a urethral orifice in the complete hypospadiac position just below the phallus, well developed labia, small vaginal orifice partially obliterated by a membrane, and no testicles palpable; 4) excessive amounts of 17-ketosteroids in the urine; and 5) at exploratory laparotomy normal tubes and ovaries, a rudimentary uterus, and generalized enlargement of both adrenal glands. Part of one adrenal gland was removed and microscopic section revealed diffuse hyperplasia of the cortex. Roentgen therapy to the adrenal glands produced no change in the patient's appearance or in the size of the clitoris after an interval of two months. Oral stilbestrol (5 mg. daily for four months) caused development of the breasts, pigmentation of the nipples, and appearance of axillary hair, but no change in the size of the clitoris; however, with smaller doses of stilbestrol for 20 months there was a definite decrease in the size of the clitoris and a decrease in the rate of growth so that the child grew at a normal rate. At this time the epiphyses were found to be nearly closed, which might have been due to stilbestrol, so the estrogen was discontinued. Plastic operations consisting of amputation of the clitoris and extension of the vaginal orifice were successfully performed at the age of seven years. Attention is called to the fact that the patient had an older sibling with identical features who died of pneumonia at the age of six years, two years before the patient was first studied. Because of this history, the androgen excretion of the patient's mother was examined and was found to be normal in amount.—E.C.R., Jr.

RUBINSTEIN, B. B. AND H. S. GUTERMAN. A simple technique for preparing vaginal smears. *Am. J. Obst. & Gynec.* 50 (5): 565-567 (1945).

The authors described in detail a simple and practical means of preparing vaginal smears which is adaptable to home and office use by the patient and for the physician.—C.D.D.

STEIN, I. F. Bilateral polycystic ovaries: significance in sterility. *Am. J. Obst. & Gynec.* 50 (4): 385-398 (1945).

The author has studied 53 patients with bilateral polycystic ovaries. The diagnosis usually was based on a typical clinical syndrome, characterized by menstrual irregularity featuring amenorrhea, presumed sterility, masculine type of hirsutism, and less consistently, retarded breast development and obesity. The diagnosis was substantiated by demonstrating the ovarian lesions with pneumoperitoneum. The authors found endocrine therapy valueless. Bilateral wedge resection and suture of the ovaries was done in all instances. There were no recurrences and 64.5 per cent of the married women became pregnant.—C.D.D.

PATTON, G. C. Diethylstilbestrol in the treatment of functional ovarian disorders. *Am. J. Obst. & Gynec.* 50 (4): 417-421 (1945).

The author treated 107 women with 232 functional ovarian complaints which included dysmenorrhea, simple cystic ovaries, irregularity in menstrual rhythm, profuse bleeding, and infertility. All patients received diethylstilbestrol, five milligrams orally daily for 20 days, therapy being started at the end of bleeding. The following results were recorded: partial or total relief in 56 per cent of dysmenorrheic patients; ovaries returned to normal size in 37 of 47 patients with cystic ovaries; in 13 of 14 patients with continuous uterine bleeding, hemostasis was produced in one to four days; 70 per cent of all menstrual disturbances were partially or entirely corrected; and in an admittedly incomplete study on infertile women, 26 per cent conceived.—C.D.D.

WATT, L. O. Endometrial biopsy curette. *Brit. M. J.* 1: 843 (1945).

An improved endometrial biopsy curette is described which is designed to give information in sterility investigations. The terminal cup is as short as possible allowing a biopsy to be taken from close to the fundus of the uterus and so give a much larger and longer strip of endometrium for histological section. The large, sharp, prominent edge of the curette cup improves the possibilities of getting an adequate sample of atrophic endometrium.—L.T.S.

WAY, S. D. B. E. in treatment of menopausal symptoms. *Brit. M. J.* 1: 10 (1946).

Eleven cases of menopausal disturbance were treated with D. B. E. Five were completely relieved of their symptoms, three were greatly improved and three failed to respond even after doses of three grams. The three patients who were improved but not completely relieved and two of the three failures were treated with stilbestrol and were almost completely relieved in three weeks after starting stilbestrol therapy. It appears from this small series that D. B. E. is probably not as effective as stilbestrol in the relief of menopausal symptoms and its sole advantage is that it needs to be administered infrequently.—L.T.S.

## HYPOPHYSIS

COOKE, R. T. Simmonds' disease due to postpartum necrosis of the anterior pituitary gland. *Brit. M. J.* 2: 343 (1945).

A case of Simmonds' disease is described in a woman aged 59 due to necrosis of the anterior pituitary dating from a confinement twenty-seven years before. The patient showed a BMR of -37 per cent and a prolonged fall and greatly delayed return of the blood sugar on the administration of 1.4 units of insulin. The urinary 17-ketosteroids were zero. The patient died of cachexia and heart failure. On autopsy the pituitary appeared as a collapsed empty shell and adenocarcinoma of the pylorus was also present.—*L.T.S.*

DE ROBERTIS, E. AND E. DEL CONTE. A cytological method for the determination of the thyrotrophic hormone of the pituitary gland. *Rev. Soc. Argent. Biol.* 20: 88 (1944).

The authors have developed a quantitative method for the assay of the thyrotrophic hormone based on the amount of intracellular colloid in the thyroid gland. They have devised a cytological coefficient, which is defined as the ratio between the number of colloid droplets  $\times 100$  and the average diameter of the follicles. The sensitivity of the method was determined as follows: Young guinea pigs were injected with various doses of thyrotrophic hormone and 30 minutes later were sacrificed. The thyroid glands were frozen in liquid air, dried by the Altmann-Gersh method and stained with aniline blue-orange G stain. The glands showed a significant increase in the intracellular colloid even when treated with as little as 0.0002 Junkmann-Scoeller units of thyrotrophic hormone. The cytological coefficient increases with the dose, and as illustrated by a curve published in the paper, there exists an approximate proportion between this coefficient and the logarithm of the dose. A "guinea pig cytological unit" is devised; this is the amount of thyrotrophic hormone injected intravenously in a young guinea pig which will produce a fourfold increase in 30 minutes in the cytological coefficient of the control animal. The authors report that this cytological method can be applied to the assay of thyrotrophic hormone in organic fluids of normal and pathological individuals.—*F.A.de laB.*

MORGAN, J. Acromegaly with pregnancy. *Proc. Roy. Soc. Med.* 38: 326 (1945).

A case of a primipara, aged 34, who had been married seven years, and who had always suffered from headaches is reported briefly. The patient had not noted any change in the size of hands or feet or in facial appearance. She was first seen when three months pregnant and with well-developed acromegaly. An x-ray of the skull revealed enlargement of the pituitary fossa suggestive of a moderate-sized tumor. The symptoms had not progressed further by the 36th week of pregnancy.—*R.C.*

PISETSKY, J. E. Pituitary adenoma associated with chronic duodenal ulcer. *J. Nerv. & Ment. Dis.* 102: 537 (1945).

The author discusses the work of Cushing and others on the relationship of diencephalic-pituitary disorders and peptic ulcer. He then presents a case of pituitary adenoma with visual disturbances which date back 24 years. For more than eight years the patient

has had a chronic duodenal ulcer. Since irradiation of the tumor six years ago, with the exception of occasional gastric complaints, the symptoms have come to a relative standstill. The association of manifestations is accounted for on the basis that disturbances in impulse formation in the cerebral cortex and hypothalamus, as a result of pressure produced by the tumor, result in increased gastric peristalsis, hypersecretion and vasoconstriction which produce ischemia and then erosions, ulcerations or perforations of the stomach wall.—*R.G.H.*

## PANCREAS

GREENBLATT, M., J. MURRAY, AND H. F. ROOT. Electroencephalographic studies in diabetes mellitus. *New England J. Med.* 234: 119-121 (1946).

A series of forty patients with uncomplicated diabetes and a series of thirty-five diabetic patients with repeated severe insulin reactions were studied for electroencephalographic abnormalities. The incidence of abnormal electroencephalograms in the series with uncomplicated diabetes was eight per cent which compares favorably with the range in unselected groups of non-diabetic persons. In the series of thirty-five patients with repeated insulin reactions eighteen showed definitely abnormal electroencephalograms. The authors conclude that the evidence supports the theory that severe repeated insulin reactions are due not only to unstable carbohydrate regulation but also to unstable cerebral function as well. They consider insulin sensitivity as evidence of an original underlying abnormality rather than a cause of the cortical changes, and that the electroencephalogram can be a definite aid in evaluating the stability of cortical function in diabetic patients.—*L.T.S.*

LIEBERMAN, A. A. Nervous and mental manifestations observed in spontaneous hypoglycaemia. (Elgin State Hospital.) *Elgin Papers.* 5: 43 (1944).

A case is presented of spontaneous hyperinsulinism due to pancreatic adenoma with chronic mental symptoms for three years and presented as recovered in the physical and mental aspects twenty months following surgery. Two cases of so-called functional hypoglycemia are presented as recovered upon dietary management alone, employing the high-protein, low-carbohydrate, moderate-fat diet. In such cases symptomatic relief may be obtained by administering carbohydrate in amounts too small to raise the blood-sugar titre. From the cases cited and evidence from the literature it appears that hypoglycemic states may manifest themselves as simulating any and all varieties of nervous and mental disorders. Emphasis is laid upon the remarkable reversibility of cerebral reactions in chronic hypoglycemia. The psychosomatic aspects of such cerebral reactions are emphasized.—*R.G.H.*

MALINS, J. M. Globin insulin: clinical trial. *Brit. M. J.* 2: 318-319 (1945).

Globin insulin was used in single daily doses in 36 cases of which 33 had had no previous treatment. All had a history of acute onset of diabetes. The diet was approximately the same for all patients. In ten cases perfect control, both clinical and biochemical, was obtained. The average dose in this group was twenty units. In sixteen cases control was



only fair. Hyperglycemia and glycosuria persisted although weight and general health were maintained. Insulin reactions frequently occurred in this group even when the dose was increased only to control the symptoms while hyperglycemia persisted. Six of this group have been changed to protamine zinc insulin with satisfactory results. In ten cases control was definitely inadequate and they were transferred to the protamine zinc insulin-regular insulin mixture. Globin insulin is considered to have a limited place in the treatment of mild and moderately severe diabetes.—*L.T.S.*

WECHSLER, H. F. AND J. I. WEIMER. Pancreatic lithiasis: a report of two cases in young adults. *Gastroenterology* 5: 181 (1945).

Two men, aged 27 and 28, respectively, had histories of digestive complaints and abdominal pain dating to the ages of ten and eight years, respectively. Bloating; nausea; vomiting; upper abdominal pain, not relieved by food and aggravated by fried and greasy foods; steatorrhea; a slight decrease in sugar tolerance; and the presence on roentgenography of multiple, irregular calcified shadows in the region of the pancreas completed the picture in each instance. One of the patients had been treated for renal colic; the other for peptic ulcer. The authors conclude that "the possibility of a pancreatic disturbance with eventual formation of demonstrable calculi must be considered in the differential diagnosis of recurrent attacks of upper abdominal pain of obscure etiology at any age period.—*T.H.McG.*

#### PARATHYROID

WIGLEY, J. E. M. AND D. HUNTER. Calcinosis in a case of chronic nephritis with secondary hyperparathyroidism. *Proc. Roy. Soc. Med.* 38: 141 (1945).

A case is reported with autopsy findings showing chronic nephritis and hyperplasia of all four of the parathyroid bodies.—*R.C.*



THE ASSOCIATION  
FOR THE STUDY OF  
INTERNAL SECRECTIONS  
PROGRAM OF THE TWENTY-EIGHTH  
ANNUAL MEETING

FRIDAY, AND SATURDAY, JUNE 28-29, 1946  
*Hotel St Francis, San Francisco, California*

GENERAL INFORMATION

*Headquarters* St Francis Hotel, San Francisco, California

*Registration* Everyone attending the meetings is requested to register. A fee of \$1 00 will be charged non members of the Association. Membership cards should be presented when registering.

*The Scientific Sessions* The Scientific sessions will be held in the Colonial Room, and programs will begin promptly on schedule. Papers presented at all meetings are planned for ten minutes and owing to the heavy schedule must be kept within this limit. Manuscripts of all papers should be submitted to the Secretary-Treasurer at the end of the presentation.

*Annual Dinner* The Annual Dinner of the Association will be held on Friday evening, June 28, at 7 30 o'clock at the St Francis Hotel in the Colonial Room preceded by cocktails at 6 30 in the Green Room.

*Council Meetings* There will be a dinner meeting of the Council, together with all officers and members of the Publication Board, on Thursday, June 27, at the St Francis Hotel at 6 00 o'clock. There will also be a Council breakfast on June 28, luncheon meeting on June 28, and luncheon meeting on June 29, for the same group. (See hotel bulletin board for location.)

*Business Meeting* The Annual Business Meeting of the Association and Election of Officers will be held at 4 15 P M, June 29, in the Colonial Room of the St Francis Hotel.

*Local Arrangements* Dr. Hans Lisser, Fitzhugh Building, Union Square, San Francisco 8, California, is in charge of the local arrangements for the meetings.

*Secretary-Treasurer* Henry H. Turner, 1200 North Walker Street, Oklahoma City 2, Oklahoma.

IMPORTANT

Due to the general shortage of paper, copies of this program are necessarily limited. In the interest of economy and to avoid disappointment and inconvenience to yourself, PLEASE BRING THIS PROGRAM WITH YOU.

# PROGRAM

FRIDAY, JUNE 28

8:30 A.M., Registration

## I. 9:30 A.M. Colonial Room

CARL R. MOORE, presiding

### 1. PSYCHOSOMATIC ASPECTS OF ENDOCRINOLOGY

FRIEDGOOD, HARRY B., *Department of Medicine, University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles.*

### 2. PSYCHIC AND ENDOCRINE FACTORS IN OBESITY

FREED, S. CHARLES, *San Francisco, California.*

### 3. CONTROL OF ENDOCRINE OBESITY

KUNDE, M. M., *Northwestern University Medical School and Out-patient Endocrine Clinic of the Cook County Hospital, Chicago.*

#### DISCUSSION

### 4. THREE UNUSUAL NON-NEOPLASTIC OVARIAN ENDOCRINOPATHIES

GOLDBERG, MINNIE B., ALICE F. MAXWELL (*by invitation*), and PEARL M. SMITH (*by invitation*), *Divisions of Medicine and Pathology, University of California Medical School, and the Hospital for Women and Children, San Francisco.*

### 5. BILATERAL CRYPTORCHIDISM IN IDENTICAL TWINS

GLASS, S. J., *Los Angeles.*

### 6. CARCINOMA OF THE TESTIS

REYNOLDS, RALPH ARTHUR, *San Francisco.*

#### DISCUSSION

### 7. PRELIMINARY REPORT ON PROTEIN-BOUND IODINE STUDIES IN THYROID DISEASES

SOLEY, MAYO H., *University of California Hospital, San Francisco.*

### 8. ANATOMICAL EVIDENCE OF THYROID HYPOFUNCTION IN ALLOXAN INDUCED DIABETES MELLITUS

BENNETT, LESLIE L. (*by invitation*), ALEXEI A. KONEFF (*by invitation*), and ADRIANNE P. APFLEGARTH (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

### 9. THE EFFECT OF ESTROGENS ON THE THYROID

GASSNER, F. X., *Colorado Experiment Station, Fort Collins.*

#### DISCUSSION

### 10. FACTORS INFLUENCING INSULIN PRODUCTION

ANDERSON, EVELYN, JOSEPH A. LONG (*by invitation*) and VIRGINIA SUTTON (*by invitation*), *Institute of Experimental Biology and Division of Medicine, University of California, Berkeley and San Francisco.*

### 11. BIOLOGICAL ASSAY OF INSULIN. OBJECTIVE DETERMINATION OF THE QUANTAL RESPONSE OF MICE.

THOMPSON, R. E. (*introduced by F. C. KOCH*), *Pharmacology Section, Armour Laboratories, Chicago.*

### 12. INSULIN RESISTANCE: A CASE STUDY.

MCGAVACK, THOS. H., SOLOMON D. KLOTZ (*by invitation*), MILDRED VOGEL (*by invitation*), and JAMES F. HART (*by invitation*), *New York Medical College, Metropolitan Hospital Research Unit, New York.*

#### DISCUSSION

## II. 2:00 P.M. Colonial Room

### 13. THE EFFECTS OF GROWTH HORMONE AND ADRENOCORTICOTROPIC HORMONE ON THE URINARY GLUCOSE AND NITROGEN EXCRETION OF DIABETIC RATS.

- BENNETT, LESLIE L (*by imitation*), and CHOW HAO LI (*by imitation*), *Institute of Experimental Biology, University of California, Berkeley*
- 14 A COMPARISON OF THE ACUTE EFFECTS OF CORTICOSTERONE AND 17-HYDROXY CORTICOSTERONE ON BODY-WEIGHT AND THE URINARY EXCRETION OF SODIUM, CHLORIDE, POTASSIUM, NITROGEN AND GLUCOSE  
INCL, DWIGHT J, RUTH SHEPARD (*by imitation*), and MARVIN H KULFNGA (*by imitation*), *The Research Laboratories The Upjohn Company, Kalamazoo*
- 15 THE ISOLATION OF A NEW ACTIVE STEROID FROM THE ADRENAL CORTEX  
LOWENSTEIN, BERTRAND E and R L ZWEMER *Department of Anatomy, College of Physicians and Surgeons, Columbia University and Department of Pharmacotherapy, Harvard University Medical School*

#### DISCUSSION

- 16 THE QUANTITATION OF AXILLARY HAIR GROWTH AS AN INDEX OF ENDOCRINE FUNCTION  
KINSEIL, L W, EDW C REIFFENSTEIN, JR, DOROTHY BRYANT (*by imitation*), and FULLER ALBRIGHT, *Oakland and Boston*
- 17 THE ASSISTANT OF SOMATIC ANDROGENY  
BAYLEY, NANCY (*by imitation*), and LEOA M BAYER, *Institute of Child Welfare of the University of California, and the Stanford University School of Medicine*
- 18 SEXUAL BEHAVIOR OF THE BOVINE MALE USED IN ARTIFICIAL INSEMINATION  
HART, G H, W M REGAN, and S W MEAD (*introduced by H H COLI*), *Division of Animal Husbandry, University of California, Davis*

#### DISCUSSION

- 19 ENDOCRINE LEADERS AND TREATMENT OF CHRONIC CYSTIC MASTITIS AND THEIR RELATION TO INFERTILITY  
MORTON, JOSIAH H, *Dept of Medicine, N Y Medical College, Flower & Fifth Avenue Hospitals—and the Endocrine Service of Dr T H McGauack at Metropolitan Hospital*
- 20 ARTIFICIAL REPRODUCTION OF THE CYCLIC CHANGES IN CERVICAL MUCUS IN HUMAN CASTRATES  
ABARBANEL, A R, *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles*
- 21 FURTHER STUDIES ON THE CONTROL OF MENORRHAGIA  
GREENBLATT, ROBERT B, *Department of Endocrinology, University of Georgia School of Medicine, Augusta*

#### DISCUSSION

- 22 FACTORS CONCERNED IN THE MAINTENANCE OF FUNCTION OF THE CORPUS LUTEUM  
NELSON, W O, *Department of Anatomy, College of Medicine, The State University of Iowa, Iowa City*
- 23 INDUCTION OF OVULATION IN THE DIESTROUS MOUSE BY GONADOTROPINS  
SAUNDERS, FRANCIS J, *Research Laboratories of G D Searle & Company, Chicago*

#### ANNUAL DINNER

### III 7 30 P M Colonial Room, Hotel St Francis

- PRESENTATION OF THE E R SQUIBB & SONS AWARD FOR 1944-45  
PRESENTATION OF THE CIBA AWARD FOR 1944-45  
PHILIP E SMITH, *Chairman of the Committee on Awards for 1944-45*  
PRESENTATION OF THE E R SQUIBB & SONS AWARD FOR 1945-46  
PRESENTATION OF THE CIBA AWARD FOR 1945-46  
WILLARD O THOMPSON, *Chairman of the Committee on Awards for 1945-46*

CARL R. MOORE, *The University of Chicago.*

SATURDAY, JUNE 29

IV. 9:00 A.M. *Colonial Room*

24. DIAGNOSIS OF HYDATIDIFORM MOLE BY GONADOTROPHIC HORMONE ASSAY USING THE SOUTH AFRICAN FROG.

WEISMAN, ABNER I., and CHRISTOPHER W. COATES (*by invitation*), *Crow Creek Hospital, Ft. Thompson and New York.*

25. THE INFLUENCE OF VARIOUS HORMONES ON THE RESISTANCE OF SWISS MICE TO ADAPTED POLIOMYELITIS VIRUS.

ANDERSON, JOHN A. and VERNON BOLIN (*by invitation*), *Department of Pediatrics, Salt Lake County Hospital, University of Utah, Salt Lake City.*

26. THE VALIDITY OF ENDOCRINE RESEARCH ON THE DOMESTIC NORWAY RAT.

RICHTER, CURT P., *Phipps Clinic, The Johns Hopkins Hospital, Baltimore.*

DISCUSSION

27. DISCUSSION OF A SIMPLE, RAPID AND PRACTICAL MEANS OF DETERMINING URINARY GONADOTROPHINS IN PATIENTS.

JUNGCK, EDWIN (*by invitation*), WILLIAM MADDOCK (*by invitation*), and CARL G. HELLER, *Departments of Physiology and Medicine, University of Oregon Medical School, Portland.*

28. GONADOTROPHINS IN NERVOUS EXHAUSTION DUE TO OVARIAN HYPOFUNCTION.

HAWKINSON, L. F., *Oakland.*

29. EQUINE GONADOTROPIN. NINE YEARS OF CLINICAL EXPERIENCE.

HALL, GEORGE J., *Sacramento.*

DISCUSSION

30. THE SYNERGISTIC ACTION OF PROGESTERONE WITH TESTOSTERONE PROPIONATE ON THE REPRODUCTIVE TRACT OF THE CASTRATE FEMALE OPOSSUM.

MORGAN, CHARLES F., *Department of Pharmacology and Materia Medica, Georgetown University, Washington, D. C.*

31. THE SOURCE OF THE EXCESS CREATINE FOLLOWING ADMINISTRATION OF METHYLTESTOSTERONE.

SAMUELS, LEO T., DOROTHY M. SELLERS (*by invitation*), and CARLEY J. MCCAULAY (*by invitation*), *Department of Biological Chemistry, School of Medicine, University of Utah, Salt Lake City.*

32. EXPERIMENTAL USE OF TESTOSTERONE IN PREMATURE INFANTS.

SHELTON, E. KOST, *The Shelton Clinic, Los Angeles.*

DISCUSSION

33. CRANIOPHARYNGIOMA WITH INFANTILISM: CASE REPORT WITH CLINICAL AND PATHOLOGICAL STUDIES.

MCGAVACK, THOS. H., RAYMOND HARRIS (*by invitation*), ANDREA SACCONI (*by invitation*) and HARRY GOLDBERG (*by invitation*), *New York Medical College, Metropolitan Research Unit, New York.*

34. CONTINUOUS GROWTH OF NORMAL RATS RECEIVING PURE GROWTH HORMONE.

EVANS, H. M. (*by invitation*), MIRIAM E. SIMPSON (*by invitation*), and CHOH HAO LI (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

35. OBSERVATIONS ON THE USE OF THE SERUM PHOSPHORUS LEVEL AS AN

INDEX OF PITUITARY GROWTH HORMONE ACTIVITY; THE EFFECT OF ESTROGEN THERAPY IN ACROMEGALY.

REIFENSTEIN, EDWARD C., JR.; LAURENCE W. KINSELL; and FULLER ALBRIGHT, *Department of Medicine, Harvard Medical School and the Medical Service of Massachusetts General Hospital, Boston.*

36. FACTORS INFLUENCING THE PRODUCTION OF CARDIO-VASCULAR DISEASES BY ANTERIOR PITUITARY AND CORTICOID HORMONES.

SELYE, HANS, *Institute of Experimental Medicine and Surgery, University of Montreal, Canada.*

DISCUSSION

V. 2:00 P.M. Colonial Room.

37. THE SUBSTANCE IN LATE PREGNANCY MARE SERUM CAUSING OVARIAN INHIBITION.

COLE, H. H., *Division of Animal Husbandry, University of California, Davis.*

38. THE PROBLEMS OF ANTIGONADOTROPINS IN CLINICAL THERAPY.

LEATHEN, J. H., and A. E. RAKOFF, *Department of Zoology, Rutgers University, New Brunswick, and the Departments of Obstetrics and Gynecology and the Endocrine Laboratory, Jefferson Medical College and Hospital, Philadelphia.*

39. END RESULTS OF TREATMENT OF PITUITARY DWARFS WITH CHORIONIC GONADOTROPIN AND SEX HORMONES.

THOMPSON, W. O., N. J. HECKEL, and P. K. THOMPSON (*by invitation*), *Chicago.*

DISCUSSION

40. ADVANTAGES OF MODIFIED PROTAMINE ZINC INSULIN IN THE REGULATION OF DIABETES.

MACBRYDE, CYRIL M., *Los Angeles.*

41. EFFECT OF IODINE INTAKE ON THYROID IODINE DISTRIBUTION AND THYROID WEIGHT OF RATS TREATED WITH THIOURACIL AND OTHER GOITROGENS.

MACGINTY, D. A., and E. A. SHARP, *Research Laboratories, Parke, Davis & Company, Detroit.*

42. THE REVERSIBLE INACTIVATION OF THYROTROPIC HORMONE. ITS INACTIVATION BY THYROID TISSUE AND REACTIVATION BY THIOURACIL AND OTHER GOITROGENIC AGENTS.

RAWSON, RULON W., ALEXANDER ALBERT (*by invitation*), JANET W. MCARTHUR (*by invitation*), PRISCILLA MERRILL (*by invitation*), BEATRICE LENNON (*by invitation*), and CHARLOTTE RIDDELL (*by invitation*), *The Thyroid Clinic Massachusetts General Hospital, Boston.*

DISCUSSION

43. SENSITIVITY OF THE REPRODUCTIVE SYSTEM OF HYPOPHYSECTOMIZED FORTY-DAY-OLD MALE RATS TO TESTOSTERONE PROPIONATE.

SIMPSON, MIRIAM E. (*by invitation*) and HERBERT M. EVANS (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

44. THE SYNDROME OF CONGENITALLY ABSENT OVARIES, WITH INFANTILISM, HIGH URINARY GONADOTROPINS AND SHORT STATURE, WITH OTHER CONGENITAL ABNORMALITIES, SUCH AS SHORT WEBBED NECK, CUBITUS VALGUS, COARCTATION OF THE AORTA, ETC., AND TABULAR PRESENTATION OF TWENTY-ONE PREVIOUSLY UNPUBLISHED CASES.

LISSE, H., L. E. CURTIS (*by invitation*), ROBERTO F. ESCAMILLA, and MINNIE B. GOLDBERG, *Division of Medicine, University of California School of Medicine, San Francisco.*

45. ADRENAL ASCORBIC ACID RESPONSE TO ADRENOCORTICOTROPIC HORMONE IN INTACT AND HYPOPHYSECTOMIZED RATS.

DISCUSSION

46. THE USE OF DESOXYCORTICOSTERONE ACETATE IN A BEESWAX MIXTURE FOR THE TREATMENT OF ADDISON'S DISEASE.  
CODE, CHARLES F. (by invitation), EDWARD H. RYNEARSON, and MARSCHELLE H. POWER (by invitation), *Section on Clinical Physiology, Division of Medicine, and Section on Clinical Biochemistry, Mayo Foundation and Mayo Clinic, Rochester.*
47. LUTEOTROPHIC ACTION OF CHORIONIC GONADOTROPHIN IN THE WOMAN.  
BROWN, W. E., and J. T. BRADBURY, *Department of Obstetrics and Gynecology, The State University of Iowa, Iowa City.*

DISCUSSION

VI. 4:15 P.M. Colonial Room

ANNUAL BUSINESS MEETING

VII. Papers read by title.

48. FURTHER OBSERVATIONS ON THE ABSORPTION OF SUBCUTANEOUSLY IMPLANTED PELLETS OF HORMONALLY ACTIVE STEROIDS.  
MCGAVACK, THOMAS H. and HERMAN REINSTEIN (by invitation), *New York Medical College, Metropolitan Hospital Research Unit, New York.*
49. ABSENCE OF RENOTROPIC ACTION OF PURE ADRENOCORTICOTROPIC HORMONE (ACTH).  
SIMPSON, MIRIAM E. (by invitation), CHOH HAO LI (by invitation), and HERBERT M. EVANS (by invitation), *Institute of Experimental Biology, University of California, Berkeley.*
50. THE RATE OF METABOLISM OF STEROID HORMONES BY THE LIVERS OF DIFFERENT SPECIES.  
SAMUELS, LEO T., and C. J. MCCAULAY (by invitation), *Department of Biological Chemistry, School of Medicine, University of Utah, Salt Lake City.*
51. THE COMPARATIVE EFFECT OF VARIOUS GOITROGENIC AGENTS ON THE COLLECTION OF RADIOACTIVE IODINE BY THE THYROID IN RATS AND CHICKS.  
RAWSON, RULON W., D. A. MCGINTY, and WENDELL PEACOCK (by invitation), *The Thyroid Clinic, Massachusetts General Hospital, Boston; the Research Laboratories, Parke Davis & Company, Detroit; and the Nuclear Physics Laboratories, Massachusetts Institute of Technology, Cambridge.*
52. TURNER'S SYNDROME. A CASE REPORT.  
MOFFAT, WILLIAM M., *The Santa Barbara Clinic, Santa Barbara.*
53. INFLUENCE OF METABOLISM ENURESIS.  
OSLUND, ROBERT M., *Ross-Loss Medical Group, Los Angeles.*
54. QUANTITATIVE INHIBITION OF OESTROGEN EFFECT ON CHICK OVIDUCT BY PROGESTERONE.  
HERTZ, ROY, *National Institute of Health, Bethesda.*
55. THE EFFECT OF SUBCUTANEOUS ADMINISTRATION AND TOPICAL APPLICATION OF STEROID PREPARATIONS TO THE PIGMENTATION AREA OF THE HAMSTER.  
KUPPERMAN, HERBERT S. *Department of Endocrinology, University of Georgia School of Medicine, Augusta.*
56. THE INFLUENCE OF THE ADRENAL CORTEX ON THE METABOLISM OF THE EVISCERATED RAT.  
ROBERTS, SIDNEY (by invitation), *The Worcester Foundation for Experimental Biology, Shrewsbury.*
57. THE NATURE OF BENADRYL ACTIVITY: GLUCOSE TOLERANCE CURVES.  
REINSTEIN, HERMAN (by invitation), and THOMAS H. MCGAVACK,

- 58 NATURE AND DISTRIBUTION OF THE SKELETAL ABNORMALITIES IN CUSHING'S SYNDROME  
AIBRIGHT, I ULLER, ANNE P FORBLS, and EDWARD C RLIFFNSTEIN, Jr, *Department of Medicine, Harvard Medical School and the Medical Service of Massachusetts General Hospital, Boston*
- 59 MANAGEMENT OF THIRTFATINED AND HABITUAL ABORTION BY LARGE DOSES OF ORAL ESTROGEN  
ABARBANEL, A R, *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles*
- 60 CLINICAL SYNDROMES OF ABERRATIONS IN CORPUS LUTEUM FUNCTION  
PARRETT, VIRGIL O (by invitation), and A R ABARBANEL, *Departments of Obstetrics and Gynecology, College of Medical Evangelists Los Angeles*
- 61 PROBLEM OF 'CLOSED GAILOPIAN TUBES' HORMONAL DIFFERENTIATION OF TUBES CLOSED BY SPASM FROM THOSE CLOSED BY ORGANIC PATHOLOGY BY MEANS OF METHYL TESTOSTERONE  
ABARBANEL, A R, *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles*
- 62 THE USE OF SODIUM PARA-AMINOBI-NOZATE PARENTERALLY IN THE TREATMENT OF HYPERTHYROIDISM  
BERMAN, LOUIS, *New York City*
- 63 HYPOGONADOTROPHIC EUNUCHOIDISM—ITS CLINICAL AND LABORATORY DELINEATION FROM OTHER FORMS OF HYPOGONADISM WITH A DISCOURSE ON TREATMENT  
HELLER, CARL G and WARREN O NISSON, *Departments of Physiology and Medicine, University of Oregon Medical School, Portland, and Department of Anatomy, University of Iowa Iowa City*
- 64 DETERMINATION OF CORTICOSTEROIDS IN URINE  
LOWENSTEIN, B E, A C CORCORAN, and IRVINE H PAGE, *Research Division, Cleveland Clinic Foundation Cleveland*
- 65 THE EFFECT OF HYPOPHYSECTOMY ON THE TIME OF LAY OF THE HFN'S Egg  
ROTHCHILD, IRVING (introduced by RICHARD M FRAPS), *Agricultural Research Center, U S Department of Agriculture Beltsville Maryland*
- 66 PARATHYROIDITIS SYNDROME IN PITUITARY BASOPHILISM  
PERLMAN, ROBERT M, *San Francisco*
- 67 DIURNAL VARIATIONS IN THE LEVELS OF BLOOD GLUCOSE OF NORMAL HUMAN BEINGS SUBJECTED TO VARIOUS TYPES OF CALORIC RESTRICTION  
SCHWINNER, DAVID (by invitation), and THOMAS H MCGAYACK, *New York Medical College, Metropolitan Hospital Research Unit, New York*
- 68 THE ROLE OF SEX HORMONES IN THE ORIGIN AND DEVELOPMENT OF ENDOMETRIAL GLANDS IN THE OPOSSUM  
MOORE, CARL R and ELIZABETH A FAIOR (by invitation), *Hull Zoological Laboratory, The University of Chicago, Chicago*

## ABSTRACTS

### ARRANGED ACCORDING TO NUMBER

#### 1 PSYCHOSOMATIC ASPECTS OF ENDOCRINOLOGY

Harry B Friedgood From the Department of Medicine of the University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles, California

Carefully conducted observations were made of cases in which emotional conflicts precipitated endocrinopathies such as exophthalmic goiter adiposogenital



dystrophy, amenorrhoea, meno-metrorrhagia, dysmenorrhoea and diabetes mellitus. Other cases were studied in which personality changes and abnormal emotional behavior resulted from hypothalamo-hypophysial tumors and from Cushing's syndrome due to adrenocortical neoplasm. These data indicate that the nervous system influences the functional activity of certain endocrine glands either by their innervation or through neuro-humoral means, and that an abnormal supply of hormones may affect the behavior pattern in certain circumstances.

Correlation of the available anatomical, physiological and clinical data discloses that the hypothalamo-hypophysial area plays an important role in the mechanism by means of which emotional conflicts directly or indirectly disturb the functional activity of certain endocrine organs.

## 2. PSYCHIC AND ENDOCRINE FACTORS IN OBESITY.

S. Charles Freed. San Francisco.

Overweight is with rare exception a non-endocrine disturbance. It is a result of a positive caloric balance in which the patient expends less calories in energy than that which is taken in. The actual number of calories required for maintenance of weight may vary widely in different individuals thus accounting for popular misconceptions. The inability to control the intake of food at that level which maintains weight is due to underlying psychic drives. This tendency may be masked for many years or may be present from infancy. Many psychic factors will increase the urge to eat and the inability to control this urge. Other factors include disturbances in the endocrine system, organic diseases and others, but they all have one thing in common in that they increase the psychic or nervous tension of the individual. The most common endocrine disturbances in this regard are the menopause and premenstrual tension, and only occasionally a thyroid deficiency. The treatment of obesity is similar to that of many psychosomatic disturbances. The first goal is that of inducing a sense of well-being in the patient by correcting any organic, endocrine or psychic disorder. In addition, benzedrine sulphate is a valuable drug for curbing the appetite and so establishing a high morale so that the patient is encouraged to continue depriving himself of the pleasure of eating. The use of thyroid is only rarely indicated, and often fails besides inducing harm from its toxic effects. Patients should receive psychiatric consultation where mild psychotherapy fails. Proper education of parents and emphasis on the psychological aspects of nutrition for children is advised.

## 3. CONTROL OF ENDOCRINE OBESITY.

M. M. Kunde. From the Northwestern University Medical School and the Outpatient Endocrine Clinic of the Cook County Hospital, Chicago.

The investigation of obesity presented in this study is characterized by the fact that all cases herein reported were previously diagnosed as obese due to some endocrine dysfunction; in addition to the adiposity some patients gave evidence of specific gonad, thyroid or other endocrine dysfunction. In the treatment no endocrine product was used as part of the reducing therapy; reduction in weight was not based on calculated caloric intake but on re-education of the patient's dietary habits.

Physical examination and laboratory tests were made both at the beginning and at the end of the period of weight reduction. In some instances the laboratory findings were checked at the time when the patient had lost 50 pounds in body weight. Laboratory tests, in most cases, included basal metabolism, urinalysis, complete blood count, glucose tolerance, blood cholesterol, calcium and phosphorus, and x-ray of the pituitary. No patients with diabetes or marked hypothyroidism were included in this study. The advice and services of dietitians were not employed. Weight reduction in these patients was handled as any other major medical problem and patients reported directly to the physician at each visit. Charts, graphs and other significant data including weight loss up to one hundred pounds are presented.

#### 4. THREE UNUSUAL NON-NEOPLASTIC OVARIAN ENDOCRINOPATHIES.

Minnie B. Goldberg, Alice F. Maxwell, and Pearl M. Smith, San Francisco. From the Divisions of Medicine and Pathology, University of California Medical School, and the Hospital for Women and Children, San Francisco.

The three cases with which this paper deals are being reported (1) because they are rare, and (2) because all were diagnosed preoperatively, verified by surgical exploration, and benefited by appropriate therapy.

##### *I. Ovarian Agenesis*

An eight-year-old girl was studied for five years because of failure to grow. Ovarian agenesis was suspected and verified by exploratory laparotomy at age thirteen. Early proof of diagnosis was sought in the hope of producing maximum growth before epiphyseal closure occurred. Stilbestrol therapy has been instituted. This is the youngest verified case on record.

##### *II. Ovarian Hyperthecosis*

An eighteen-year-old girl with primary amenorrhea, heterosexual hypertrichosis, virilism, aene and impaired carbohydrate tolerance had bilaterally enlarged ovaries. Hyperthecosis of the ovaries was suspected and proved pathologically. Bilateral partial ovarian resection resulted in prompt onset of normal and regularly recurring menses for the past year, and some improvement of the hypertrichosis, aene and carbohydrate tolerance.

##### *III. Precocious Puberty*

A six-year-old girl with evident secondary sex characteristics and an adult sized uterus bled per vaginam for eleven days. By exclusion an ovarian tumor was diagnosed despite lack of palpatory evidence. Surgical removal of a unilateral, enlarged, polycystic ovary was followed by regression of all signs of precocious puberty.

#### 5. BILATERAL CRYPTORCHIDISM IN IDENTICAL TWINS.

S. J. Glass. From the Endocrine Clinic—Cedars of Lebanon Hospital, Los Angeles, California.

The infrequency of reports of congenital sexual anomalies in twins prompts this report. A pair of identical twins presented themselves at age 9 with bilateral cryptorchidism. This was associated with mild stunting of growth and a poor nutritional status. There were no other significant anomalies. Treatment was directed to (1) attempts to induce spontaneous testicular descent with the aid of chorionic gonadotropin,—later supplemented with testosterone propionate and methyl testosterone in minimal dosage, (2) improvement in nutrition. In two years of observation there was unilateral descent of the contralateral testis in each boy and descent to the external inguinal ring of the other testis. Considerable acceleration in skeletal and phallic growth accompanied the testicular descent. The nutritional status was likewise improved. Absence from the clinic has prevented further treatment.

#### 6. CARCINOMA OF THE TESTIS.

Ralph Arthur Reynolds. San Francisco, California.

Zondek, 1930, was the first to report that tumors of the testicle cause increased excretion of the gonadotropic hormone. This discovery has greatly accelerated interest in early diagnosis and treatment of tumors of the testis. The question of pathogenesis remains unchanged. There is still considerable confusion concerning the classification of testicular neoplasms. Correlation between their structure and the hormonal test is resulting in better classification. Chorion epithelioma causes five times the excretion of prolan A as noted in embryonic carcinoma. Persistence of prolan A excretion after excision of the tumor or after irradiation is presumptive evidence of metastasis and therefore of unfavorable prognosis.

A review of a study by Hinman of 85,000 male admissions to San Francisco

County and University of California Hospitals showed proved tumors of the testis in 52 or 1:1600. The relative frequency of testicular tumor among malignant tumors of all kinds is about 0.57%. Bilateral involvement, usually in cryptorchidism, is rare. The large majority of patients are between twenty and forty years. Julien, in 1925, collected 139 cases in infants. About 50% of testicular tumors belong to the differentiated type of the carcinomatous group of embryonal tumors. These afford the best prognosis. Primitive types of the carcinomatous group of embryonal tumors are highly malignant and offer a poor prognosis, although highly sensitive to irradiation. Radical surgical treatment of observed metastasis is of no use. Intensive irradiation alone is indicated.

#### *Report of Two Cases*

1. Twenty-seven year old male—Orchidectomy performed within three weeks after first observation by the patient. Patient living and well ten years later.

2. Thirty year old male—Reported swelling three and one-half months after first noted by patient. Extensive metastases already present, intensive irradiation instituted. Patient died eighteen months after orchidectomy. Both cases revealed tumors of adeno-carcinoma pattern.

#### 7. PRELIMINARY REPORT ON PROTEIN-BOUND IODINE STUDIES IN THYROID DISEASES.

Mayo H. Soley. University of California Hospital, San Francisco.

The determination of the protein-bound iodine in the serum of approximately 400 patients with various types of thyroid disease correlate well with the patients' clinical status and other indirect tests such as the basal metabolic rate, the plasma cholesterol and the oral galactose tolerance test. Sources of error such as previous administration of organic iodine (Priodax and other dyes for gall bladder visualization; Diodrast, Hippuran, Neo-Ipax, Skiodan, Lipiodol and other diagnostic agents) must be recognized.

Follow-up studies in patients with either Graves' disease or hypothyroidism indicate that the return of the clinical status to normal is associated with a similar reversion of the protein-bound iodine to normal levels.

#### 8. ANATOMICAL EVIDENCE OF THYROID HYPOFUNCTION IN ALLOXAN INDUCED DIABETES MELLITUS.

Leslie L. Bennett, Alexei A. Koneff and Adrienne P. Applegarth. Institute of Experimental Biology, University of California.

Male rats were rendered diabetic by the intraperitoneal injection of alloxan. There was a reduction in both the relative and absolute thyroid weights in diabetic animals that was most marked in those with sustained severe diabetes. The mean thyroid weight of animals with diabetes of one month's duration was 16.0—0.8 mgm as compared with 40.3—2.6 mgm for the controls of the same age. Histologically the glands were characterized by small follicles, flattened epithelium, smaller and more darkly stained nuclei, and decreased vascularity. The Golgi apparatus was smaller and less elaborate and appeared as a small cap above the nucleus without the perinuclear extension seen in the normal control. The mitochondria were reduced in number and lost their tendency to be concentrated in the cytoplasm nearest the cell.

#### 9. THE EFFECT OF ESTROGENS ON THE THYROID.

F. X. Gassner. Colorado Experiment Station, Colorado State College, Fort Collins.

The thyroids, ovaries and uteri of 104 female rats were examined histologically to determine the effects of continued administration of natural and synthetic estrogens upon these organs, and to obtain information regarding thyroid-ovarian relationship. The animals were kept on a goitrogenic diet, low in iodine, and 3 out of the 6 groups received iodine in the form of KI. Four groups received either 30 gamma estrone or 9.4 gamma stilbestrol daily. The hyperplastic goiter produced in rats on the low-iodine diet was alleviated following administration of iodine. Estrogens given to rats on low-iodine diet reduced the goiter but caused

some degeneration of the thyroid parenchyma and lowered iodine storage. Of the two estrogens, diethylstilbestrol was more effective in this respect than was estrone. The storage of iodine in the thyroid glands of rats on low-iodine diet was not interfered with by estrogens when additional iodine was administered daily. This suggests that the effect of iodine on the thyroid is direct and not over the pituitary.

Epidermoid metaplasia occurred in the thyroids of all estrogen-treated rats. It is concluded that metaplasia was caused by the action of estrogens either upon the epithelium of pre-existing follicles because of their cellular duality, or upon embryonal remnants of the resorbed ultimobranchial body. It is not considered likely that an avitaminosis-A was present nor that a deficiency of this vitamin caused the metaplasia observed. The ovaries and uteri of the control rats were essentially normal. The ovaries of rats treated with estrogens showed severe atrophy, follicular atresia, interstitial fibrosis and occasional sub-mesovarial cyst formation. Corpora lutea were generally absent. The uteri of estrogen-treated rats showed squamous metaplasia of the endometrium with desquamation, vacuolar or hydropic degeneration and epithelial tufting. These changes varied in extent from small, focal lesions to total metaplasia of the entire lining of the uterine lumen. The few glands present were also altered.

The significance of certain pathological lesions found is discussed in the light of evidence presented by other workers. It is considered possible that some of the metaplastic areas may constitute a stage in the formation of precancerous foci.

#### 10. FACTORS INFLUENCING INSULIN PRODUCTION.

Evelyn Anderson, Joseph A. Long, and Virginia Sutton. Institute of Experimental Biology and Division of Medicine, University of California, Berkeley and San Francisco.

With the use of a small perfusion pump circulation was maintained in the isolated rat pancreas (including also the stomach, duodenum and mesentery) for two hours. Evidence of a living organ was demonstrated by its utilization of oxygen and glucose and by the stimulation of insulin production when the glucose in the blood perfusate was raised to 300 mg. per cent. The assay of insulin in the blood perfusate was done on demedullated, alloxan-treated, hypophysectomized rats.

Studies are being made to determine what conditions besides hyperglycemia will stimulate insulin production directly. A purified growth hormone preparation added to the perfusate did not stimulate the pancreas to produce insulin.

#### 11. BIOLOGICAL ASSAY OF INSULIN. OBJECTIVE DETERMINATION OF THE QUANTAL RESPONSE OF MICE.

R. E. Thompson (Introduced by F. C. Koch). Pharmacology Section, Armour Laboratories, Chicago.

A simple method is described for the objective determination of the presence or absence of advanced insulin symptoms in mice. The method is utilized in the biological assay of insulin to eliminate personal bias and to reduce the cost of assay by making possible the further use of mice which would ordinarily be discarded. Personnel requirements are also reduced because the close observation of mice ordinarily required is eliminated.

The method consists of placing appropriate insulin treated groups of mice on separate 60° sloped wire mesh screens (24" x 36"). A hundred or more mice may be placed on each such screen. The screens must be arranged so that the mice can come off only over a free edge 8 inches or more from any surface. The mice will remain on the screen until advanced insulin symptoms (convulsion, coma, muscular weakness) cause them to lose their foothold. They will then fall from the free edge of the screen into suitable trays after which they may be injected with glucose solution so they will recover for use in subsequent assays. Two hours after injection the mice remaining on the screens are counted. Difference from the original number gives the number of positive reactions. The customary treatment of these values gives the estimated potency of the sample insulin in terms of a standard.

Over 100 assays (200 mice each) have been completed by this procedure at room temperature. The procedure is shown to be equivalent in precision to the

usual procedure of detecting positive reactions by observation of mice in ordinary temperature controlled compartments.

This "sloped screen" procedure is adaptable to either room temperature or elevated temperature operation.

It is pointed out that this procedure for objectively determining a physiological "end-point" may be adaptable to other problems such as the bioassay of adrenocorticotropin and adrenocortical extract by anti-insulin activity and the quantitative study of hypnotics and anesthetics.

## 12. INSULIN RESISTANCE: A CASE STUDY.

Thomas H. McGavack, Solomon D. Klotz, Mildred Vogel and James F. Hart. N. Y. Medical College, Metropolitan Hospital Research Unit.

A 64 year old man, whose diabetes began 7 years ago, demanded at that time as much as 920 units intramuscularly and 400 units intravenously daily to overcome glycosuria and ketonuria. Later he was able to do without insulin for 3 years. A second and a third period of "insulin insensitivity" have been observed, each associated with severe local reactions to insulin injections. As a result of studies during this third period, allergic antibodies to insulin were demonstrated repeatedly by the Kustner-Prausnitz method for passive transfer of sensitivity. Such reactions disappeared in from 10 to 12 weeks after the discontinuance of insulin and reappeared within from 10 days to 2 weeks upon resumption of the same. 'Benadryl' protected the patient from the development of insulin resistance due to these antibodies but did not cause their disappearance.

Effort was made to determine the presence of other substances in the blood and tissues of this patient which possessed a direct anti-insulinic action capable of protecting mice from ordinarily fatal doses of insulin. All attempts to demonstrate such a substance have failed, even when the patient was receiving 400 units of insulin daily and showing ketonuria and glycosuria of high degree.

It is concluded that insulin may act as an allergen; the development of antibodies may be so great that severe resistance to the action of insulin results. The data are discussed in relation to previous concepts of insulin resistance as revealed in the literature.

## 13. THE EFFECTS OF GROWTH HORMONE AND ADRENOCORTICOTROPIC HORMONE ON THE URINARY GLUCOSE AND NITROGEN EXCRETION OF DIABETIC RATS.

Leslie L. Bennett and Choh Hao Li. Institute of Experimental Biology, University of California.

Rats with persistent diabetes mellitus induced by alloxan were maintained on a constant food intake in metabolism cages. Urinary nitrogen and glucose were determined daily. The effects of three mgm per day of growth hormone and adrenocorticotropin hormone were studied. In each of thirteen experiments adrenocorticotropin hormone increased the degree of glycosuria and nitrogen excretion both with and without exogenous insulin administration. The increase in urinary glucose was greater than could be accounted for by gluconeogenesis from the extra protein catabolized under the influence of adrenocorticotropin hormone as measured by the rise in urinary nitrogen.

In seven of eight experiments without exogenous insulin, and in each of five experiments with exogenous insulin, growth hormone promoted protein storage as indicated by a decrease in urinary nitrogen excretion. In only five of the thirteen experiments with growth hormone was there a significant increase in glycosuria.

There is, therefore, in rats with alloxan induced diabetes a clear cut separation between the metabolic effects of growth hormone and adrenocorticotropin hormone. Only the adrenocorticotropin hormone produced a typical exacerbation of the diabetes with enhancement of both glycosuria and nitrogen excretion.

## 14. A COMPARISON OF THE ACUTE EFFECTS OF CORTICOSTERONE AND 17-HYDROXY-CORTICOSTERONE ON BODY WEIGHT AND THE URINARY EXCRETION OF SODIUM, CHLORIDE, POTASSIUM, NITROGEN AND GLUCOSE.

Dwight J Ingle Ruth Sheppard and Marvin H Kuzenga The Research Laboratories, The Upjohn Company, Kalamazoo

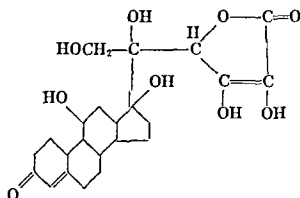
Normal male rats were force fed a high carbohydrate diet Five rats (total of 40) were tested at each dosage level of each of the two steroids The administration of 5 mgm per day for five days of either corticosterone or 17-hydroxy corticosterone caused the excretion of glucose by some of the rats and a loss of weight and an increased excretion of sodium chloride, potassium and nitrogen by all of them The responses to the 17-oxygenated compound were greater than the responses to corticosterone At dosage levels of 0.5, 1, and 2 mgm per day for three days no glucose was excreted At each dosage level 17-hydroxy corticosterone caused a loss of weight and an increased excretion of electrolytes and nitrogen to an extent which was proportional to the dose At a dosage level of 2 mgm per day corticosterone caused some inhibition of weight gain but did not have a consistent effect on the excretion of electrolytes and nitrogen At dosage levels of 0.5 and 1 mg per day, corticosterone caused some retention of sodium and of chloride but there was little effect on the excretion of potassium and nitrogen

# 15 THE ISOLATION OF A NEW ACTIVE STEROID FROM THE ADRENAL CORTEX

Bertrand E Lowenstein\* and R L Zwemer\*\* From the Department of Anatomy, College of Physicians and Surgeons Columbia University and the Department of Pharmacotherapy, Harvard University Medical School

An attempt has been made to isolate an active compound from aqueous extracts of adrenal glands Fresh adrenal glands were extracted with  $\text{CHCl}_3$  in the presence of enough anhydrous  $\text{Na}_2\text{SO}_4$  to remove all the water present The extract was purified of inactive steroids by repeated distribution between water and benzene, and the active material finally adsorbed on a precipitate of colloidal  $\text{FeSO}_4$  from an aqueous-alcoholic solution

Purification of the active material thus adsorbed has resulted in the separation by fractional crystallization of dehydrocorticosterone, and of two hitherto unsolubilized compounds whose combined activity accounts for about 80% of the activity of the original aqueous extract One of these compounds has been further characterized and is a ketonic steroid with empirical formula  $\text{C}_{21}\text{H}_{31.35}\text{O}_9$  On mild hydrolysis in the absence of air ascorbic acid has been isolated and identified chemically and biologically Oxidation with periodic acid or chromic acid yields adrenosterone The following structural formula is tentatively ascribed to it



Tests of the activity of this compound indicate that it is as active or more active than desoxycorticosterone in life maintenance, somewhat less active in its effect on sodium retention, and about equal to dehydrocorticosterone as far as carbohydrate activity is concerned

# 16 THE QUANTITATION OF AXILLARY HAIR GROWTH AS AN INDEX OF ENDOCRINE FUNCTION

Laurance W Kinsell, Edw C Reifenstein Jr, Dorothy Bryant, and Fuller Albright Massachusetts General Hospital, Boston

\* Present address Research Division, Cleveland Clinic

\*\* Present address Assoc Chief, Division of Cultural Relations, State Department, Washington, D C

The growth of axillary hair has been quantitated in normal individuals, and in patients with various endocrinopathies. The work was undertaken on the hypothesis that there would be a direct correlation between the growth of genital hair and the excretion of 17 keto-steroids. This has been found to be true only in certain categories. There was however, found to be a direct correlation between the growth of axillary hair, and the local and systemic administration of androgen. Considerable data on axillary hair growth in idiopathic and endocrine hirsutism is presented, and correlated with keto-steroid out-put, and other objective laboratory data.

On the basis of the data so far obtained, it is felt that the quantitation of genital (axillary) hair represents a simple diagnostic measure of considerable usefulness in the evaluation of endocrinopathies.

#### 17. THE ASSESSMENT OF SOMATIC ANDROGyny.

Nancy Bayley, and Leona M. Bayer. From the Institute of Child Welfare of the University of California, and the Stanford University School of Medicine.

A rating scale has been devised for assessing somatic androgyny in almost mature boys and girls. Standards are presented by body photographs; descriptions; a rating chart for constructing individual profiles. Subjects are rated according to degree and direction of sexual differentiation. Agreement between independent raters shows the scale to be reliable.

Scores fall into a bi-modal continuum with small amounts of overlapping of sexes. Cases with intermediate scores may be either undifferentiated (asexual), or show characteristics of the opposite sex (bisexual).

Androgyny appears to be truly a "mosaic," as Draper so aptly labeled it. Valid sex differences, having little or no overlap between masculine and feminine scores are almost entirely independent of each other within a sex. Many individuals may deviate in a few characteristics; few will deviate in many.

With standards for assessing somatic androgyny it should be possible to determine its relation to personality structure. Significant personality differences may well be found between those with normal builds; with relatively immature builds; with build characteristics of the opposite sex. Perhaps androgyny scores will also prove useful in relating sex variations in physique to other aspects of body build; to physical fitness; to hormone assays.

#### 18. SEXUAL BEHAVIOR OF THE BOVINE MALE USED IN ARTIFICIAL INSEMINATION.

G. H. Hart, W. M. Regan and S. W. Mead (Introduced by H. H. Cole).  
Division of Animal Husbandry, University of California, Davis.

Artificial insemination is now widely used in many countries of the world on several species of domestic animals, particularly dairy cattle and sheep. The techniques have been extensively studied and are reasonably well standardized.

One of the serious limiting factors is the behavior of the male in semen collection. Sexual libido, quality and quantity of the ejaculate and longevity of sperm activity are all factors subject to great variation within short periods of time in the same animal. Each animal manifests distinctly individualistic characteristics. Heredity and environment are both involved and need to be differentiated. Factors for sterility are evidently involved with good blood lines for production. Proven sires for transmitting ability with high fertility are to be desired in order to eliminate tendency toward male sterility. The paper sets forth the problem with some data without answering the questions involved.

#### 19. ENDOCRINE FEATURE AND TREATMENT OF CHRONIC CYSTIC MASTITIS AND THEIR RELATION TO INFERTILITY.

Joseph H. Morton. From the Department of Medicine, N. Y. Medical College, Flower and Fifth Avenue Hospitals—and the Endocrine Service of Dr. T. H. McGavack at Metropolitan Hospital.

Mammary growth and development have been shown to be dependent largely upon the ovarian hormones. In general it has been accepted that estrogens mediate

the development of the mammary ducts and progesterone that of the lobular alveoli. The role played by the anterior pituitary is still not entirely clear.

The breast, like the endometrium, cyclically shows a proliferative phase induced by estrogens, and a secretory phase stimulated by progesterone. Excessive estrogenic activity, relative or absolute (with an associated diminution in progesterone), may result in abnormal changes known as chronic cystic mastitis.

The author stresses the frequent coincidence of chronic cystic mastitis and infertility in a group of women showing no gross pelvic pathology. In these patients special tests such as the basal metabolic rate, postcoital examination, tubal insufflation test and the seminal fluid were normal. The endometrial biopsies, however, showed evidence of hyperestrinism. The author concludes that the endometrial and mammary abnormalities are both manifestations of disturbed estrogen-progesterone balance.

Several methods of hormonal therapy, and also the place of irradiation and surgery in the management of chronic cystic mastitis are discussed and evaluated. Chorionic gonadotropin was found to be the most effective method of therapy.

## 20 ARTIFICIAL REPRODUCTION OF THE CYCLIC CHANGES IN CERVICAL MUCUS IN HUMAN CASTRATES

A. R. Abartanel, Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles

By means of estrogen (estradiol, diethylstilbestrol, hexestrol, estrone) the castrate's cervix was stimulated to secrete a clear glairy mucus which human sperm were able to penetrate and migrate through.

When progesterone or ethinyl testosterone (andhydroxyl-progesterone) was given, the mucus became more viscous, decreased in volume, while sperm either were unable to penetrate or if they did, they soon bogged down. The relationship of these findings to the cervical factor in infertility is discussed.

## 21 FURTHER STUDIES ON THE CONTROL OF MENORRHAGIA

Robert B. Greenblatt, University of Georgia School of Medicine, Department of Endocrinology, Augusta, Georgia

1. The examination of the endometrium soon after arrest of menorrhagia by estrogenic therapy usually reveals a hyperplastic or a proliferative endometrium.

2. When moderate doses of androgenic therapy are employed and bleeding is arrested, the endometrium is maintained apparently in the same status as prior to therapy.

3. When progesterone therapy is used and bleeding is arrested "according to plan," i.e. about 7-10 days after cessation of therapy, shedding of the endometrium occurs comparable to that which occurs with normal physiologic menstruation. However, the loss of blood during the 7-10 day period may be excessive.

4. The administration of 25 mg. of testosterone propionate and 10 mg. of progesterone daily over a three day period results in almost immediate cessation of bleeding which, after an interval of 4 or 5 days is followed by a short bout of withdrawal bleeding.

5. In the study, over a period of many years, of functional uterine bleeding, this method of therapy has thus far proved the most promising and ideal in the management of menorrhagia.

## 22 FACTORS CONCERNED IN THE MAINTENANCE OF FUNCTION OF THE CORPUS LUTEUM

Warren O. Nelson, University of Iowa College of Medicine, Iowa City

Estrogenic hormone appears to be a factor in the maintenance of functional activity in the corpora lutea of some species although the nature of this relationship may not be constant in the various forms. Administration of estrogen to adult female rats resulted in the maintenance of luteal function for 15 to 20 days, but did so only in the presence of the hypophysis. Removal of the hypophysis at any time during the course of treatment, i.e., during the course of pseudopregnancy, was followed by a return of the vaginal smear to an estrous state within a few days, as was true if the ovaries were removed.



Animals in which the hypophyses were removed during the course of pseudopregnancy, estrogen treatment being continued, returned to estrus when FSH, LH, chorionic gonadotrophin or pregnant mare serum were given. However, the administration of lactogenic hormone in such animals maintained the pseudopregnant state for as long as 20 days post-hypophysectomy. Suspension of treatment at any time in such animals was followed by the occurrence of vaginal estrus within three days. Animals sacrificed during the period of pseudopregnancy showed large corpora lutea, well-developed mammary glands, and mucified vaginae. Suitable stimulation of the uteri of pseudopregnant animals was followed by the development of deciduomata.

The effectiveness of preparations of lactogenic hormone in maintaining corpora lutea is attributed to the presence of the luteotrophic factor. The latter appears to be identical with the lactogenic hormone since the preparations show parallel activity of the two factors.

## 23. INDUCTION OF OVULATION IN THE DIESTROUS MOUSE BY GONADOTROPINS.

Francis J. Saunders. From the Research Laboratories of G. D. Searle & Co., Chicago.

Various gonadotropins were compared as to their ability to produce uterine weight increases in immature rats and ovulation in adult diestrous mice. After standardizing various preparations on the basis of their effectiveness in increasing uterine weight in immature rats, it was found that about 9 R.U. of pregnancy urine extract were required to cause ovulation in 50% of the mice, or about 4 or 5 R.U. of pregnant mare's serum. Extracts of pituitaries prepared by the same method, but from glands from different species, were studied as were also various types of extracts from sheep pituitary glands. It was found that 0.1 to 1.5 R.U. of the various pituitary extracts evoked ovulation in 50% of the mice.

## 24. DIAGNOSIS OF HYDATIDIFORM MOLE BY GONADOTROPHIC HORMONE ASSAY USING THE SOUTH AFRICAN FROG.

Abner I. Weisman and Christopher W. Coates (Ft. Thompson, S. Dak.) & (New York).

A simple and rapid method of assaying large amounts of chorionic gonadotrophic hormone excreted in the urine of patients with a suspected chorionic tumor (hydatidiform mole) is presented. By means of injecting varying dilutions of the suspected urine into pairs of the South African Frog (*Xenopus laevis*) a six-hour response is obtained. The reaction is an extrusion of ova following injection of the urine containing the hormone. The method used is to dilute the urine 1:10 and 1:100 and then inject one cubic centimeter of each dilution into each of two frogs. If the 1:100 dilution causes extrusion of ova in the frogs, the amount of gonadotrophic hormone can be assumed to be present in at least 100,000 frog units per liter. No other condition, but chorionic tumors of the hydatid variety, will evoke such a strong hormone response. This test may then be assumed as a specific test for hydatidiform mole. Six cases are reported to cite the pre-operative diagnosis by this method.

## 25. THE INFLUENCE OF VARIOUS HORMONES ON THE RESISTANCE OF SWISS MICE TO ADAPTED POLIOMYELITIS VIRUS.

John A. Anderson and Vernon Bolin. Dept. of Pediatrics, University of Utah, School of Medicine, Salt Lake City.

The nature of autarceologic immunity in man and animals to poliomyelitis virus is unknown. Spontaneous mouse poliomyelitis virus (Theilers) may infect 100% of Swiss mice yet only one in 2,000 animals succumb to paralysis. It is generally believed that a sub-clinical form of poliomyelitis affects the majority of a human urban community with development of only occasional paralytic conditions. Since estrogen treatment of animals reduces mortality from intranasal doses of an adapted poliomyelitis virus it has been suggested that physiological disturbances in metabolism of hormones may play a role in the autarceologic immunity of man.

Swiss mice capable of being orally infected with the adapted poliomyelitis virus (Jungeblut-Dalldorf MM strain) were treated with desoxycorticosterone acetate, progesterone, t-propionate and stilbesterol and the mortality rate to orally administered virus determined. Control and experimental animals were fed a dose required to kill 68% of the animals.

It was found that protection against the orally administered virus was provided in the following declining order—progesterone (complete protection), stilbesterol (mortality reduced from 68% to 2.5%), t-propionate (68% to 20%); desoxycorticosterone acetate failed to modify mortality.

It is possible that these substances modify mucous surfaces, preventing entry of the virus into the body, or stimulate effective immune responses.

## 26. THE VALIDITY OF ENDOCRINE RESEARCH ON THE DOMESTIC NORWAY RAT.

Curt P. Richter. Phipps Clinic, Johns Hopkins Hospital, Baltimore.

Evidence gathered during the past few years indicates that the domestic Norway rat commonly used for all types of research in endocrinology and allied fields may be nothing more than an artificial creation of the laboratory experimenter produced by a long period of selective breeding under unnatural conditions.

This statement is based on comparisons made between domestic Norways and many thousand wild Norway rats recently trapped from the streets and alleys of a large city. These comparisons have revealed the existence of great differences in the anatomy, physiology, and responses to drugs in these two forms.

One of these differences which is of special interest to endocrinologists concerns the anatomy and function of the adrenal glands. In the domestic Norway the gland is about one-third as large as it is in the wild rat owing to a great atrophy of the cortex. (The medullas are about the same size.)

Adrenalectomy in the wild rat produces a much more pronounced state of shock. Even when they receive an amount of salt which suffices for domestic rats, these wild rats do not survive. They refuse to eat or drink, and die within two weeks. Clearly the adrenal cortex plays a much more important part in wild rats with their marked tension, fear, and anxiety, than it does in the tame, placid, domestic rats. Experiments are in progress to determine which of the various cortical extracts and in what amounts will be required to keep these rats alive. Clearly maintenance after adrenalectomy is a much more difficult problem than in the domestic rat.

A few of the other differences are that thiourea which has such a pronounced effect on the thyroid gland kills the domestic rat in doses as low as 3-5 mg. per kilogram body weight while 1-2 grams per kilogram body weight are required to kill a wild Norway rat.\* Audiogenic stimulation which has no effect on the wild Norway throws the domestic Norway into violent and usually fatal fits and convulsions.

Thus it is possible that much of the research done on the domestic rat will have to be repeated and checked on the more normal wild Norway.

Simple methods for trapping, handling, and housing wild Norway rats will be described.

## 27. DISCUSSION OF A SIMPLE, RAPID AND PRACTICAL MEANS OF DETERMINING URINARY GONADOTROPHINS IN PATIENTS.

Edwin Jungck,\* William Maddock, and Carl G. Heller. Departments of Physiology and Medicine, University of Oregon Medical School, Portland.

Simplicity, rapidity and efficiency are three prime criteria by which any method of assaying urinary gonadotrophins from patients must be judged, if such a method is to be widely adopted in clinical laboratories. Concentrating gonadotrophins from urine by filtering them through collodion membranes using pressure, dissolving the membranes, and then dissolving the active precipitates (as suggested

\* Dieke, S. H. and C. P. Richter: Acute Toxicity of Thiourea to Rats in Relation to Age, Diet, Strain and Species Variation. *Journal of Pharmacology and Experimental Therapeutics*, 83: 195, No. 3, March, 1945.

\* Schering Research Fellow in Endocrinology.

by Gorbman) satisfies the requirements of simplicity and rapidity. To test the efficiency and practicability of this procedure, it was compared with recovery of gonadotrophins using the alcohol precipitation—dialysis—alcohol reprecipitation method.

Urinary gonadotrophin titers of normal males and females, and of patients having a wide variety of syndromes causing both high and low titers were compared. The results indicate that the recovery is less complete using the membrane technic; yet it is sufficiently great and simple to provide an excellent laboratory aid to clinical diagnosis of endocrine disorders.

Details of the method along with gonadotrophic hormone analyses of interesting cases will be presented.

## 28. GONADOTROPHINS IN NERVOUS EXHAUSTION DUE TO OVARIAN HYPOFUNCTION. L. F. Hawkinson. Oakland.

As in the menopausal syndrome, ovarian hypofunction previous to the climacteric often produces distressing symptoms. Equine gonadotrophin, used chiefly in the treatment of menstrual disturbances and sterility was employed in the present series of 460 cases. These patients complained of unpleasant symptoms which included nervousness, fatigability, headache and depression. The ovarian deficiency was usually temporary, nearly one-third followed pregnancy. Vaginal spreads were an aid in diagnosis, as well as in evaluation of treatment. When the syndrome was severe and in those with undesired sterility, one-two cyclic gonadotrophin therapy was used. Although the accompanying menstrual disorder was often corrected when symptoms were relieved, subjective symptoms tended to respond more readily. Subjective symptoms were relieved in 52.6%, and improvement was noted in 32.1%.

## 29. EQUINE GONADOTROPIN: NINE YEARS OF CLINICAL EXPERIENCE. George Joyce Hall. Sacramento.

Obviously different from the human gonadotropin factor of the anterior portion of the pituitary gland, equine gonadotropin seems at times to have stimulating clinical effects on hypofunctioning human ovaries.

Over twelve hundred patients have received P.M.S. (pregnant mare's serum) for the control of menstrual disturbances and sterility due to hypo-ovarian function during the past nine years.

We insist on the proper "preparation" of the patient before administration of the serum is justified. Control of the "symptoms" by substitution therapy, and obtaining a relatively normal phase of vaginal cornification on the 18th to 23rd day of the ovarian cycle is considered necessary before there is any reason to expect the P.M.S. to cause any improvement of ovarian function. Adequate clinical tests have been made of all patients before and throughout the therapy.

Statistical tables showing results of treatment will be presented, and an effort made to determine the percentage of those whose ovarian function seems normal, but who do not remain stabilized long enough without therapy to be properly classified as "cured."

Results obtained not only justify continued use of P.M.S. for the treatment of hypo-ovarian functional conditions, but seem to indicate more satisfactory results than are obtainable with any other gonadotropin therapy.

## 30. THE SYNERGISTIC ACTION OF PROGESTERONE WITH TESTOSTERONE PROPIONATE ON THE REPRODUCTIVE TRACT OF THE CASTRATE FEMALE OPOSSUM. Charles F. Morgan. Department of Pharmacology and Materia Medica, Georgetown University, School of Medicine, Washington, D. C.

Progesterone administered alone in 1 mg and 5 mg daily doses for twelve days to the castrate female resulted in a significant decrease in the weight (56%) and size of the reproductive tract as compared with the untreated castrate. The greatest decrease in size and weight was in the uterus.

Testosterone propionate administered alone for twelve days in 1 mg daily doses

did not significantly alter the weight or size of the tract but histological studies showed that the tissues were mildly stimulated. T-propionate given in 5 mg daily doses caused the weight and size to increase over the untreated castrate.

Progesterone, 1 mg/day, and t-propionate, 1 mg/day, given simultaneously for twelve days resulted in a synergistic action which increased the weights of the Mullerian duct derivatives of the reproductive tract to about 4 times those of the untreated castrate, about 8 times those of the castrate treated with the same dosage of progesterone alone, and about 4 times those which received the same dosage of t-propionate alone. The derivatives of the urogenital sinus were also affected by a combination of the two hormones, but to a lesser extent than were Mullerian duct derivatives. The synergism was also present when the daily dosage of t-propionate was increased to 5 mg in combination with 1 mg of progesterone.

Under the conditions of this experiment, (1) progesterone administered alone has no stimulating effect, but appears to cause regressive changes in the reproductive tract, (2) androgens administered alone show a stimulating effect, (3) a synergism between progesterone and t-propionate is manifested when the two hormones are administered simultaneously, and (4) progesterone apparently enhances the action of the androgen.

### 31. THE SOURCE OF THE EXCESS CREATINE FOLLOWING ADMINISTRATION OF METHYLTESTOSTERONE

Leo T. Samuels, Dorothy M. Sellers, Carley J. McCaulay, Department of Biological Chemistry, University of Utah, Salt Lake City

Since creatinemia and creatinuria do not follow administration of methyltestosterone in other animals, experiments were carried out on human beings with diseases of certain organs that might be involved in creatine metabolism. The following groups were studied: normal subjects, patients with severe liver damage, patients with nephrosis, and patients with severe nephritis. Blood and urine samples were collected before administration of methyltestosterone, after ten days of medication and at the end of twenty days' treatment with the drug. In the normal individual the plasma creatine was generally elevated at the end of the first ten days but in adult males creatinuria did not always appear because of the low original creatinemia. Creatinemia appeared earlier in women and children, but in all cases the creatine threshold lay between 0.7 and 1 mg/100 cc plasma. Creatinemia and creatinuria were produced in the cases suffering with hepatic damage, even when in a terminal condition. Creatinemia also appeared in the group suffering with nephrosis. The only cases where no large increase in plasma creatine occurred were those suffering with severe nephritis. Apparently the kidney is a primary factor in the excess creatine found after administration of methyltestosterone.

### 32. EXPERIMENTAL USE OF TESTOSTERONE IN PREMATURE INFANTS

E. Kost Shelton, Los Angeles

Because of the nitrogen storage factor and other physiologic properties attributed to testosterone, preparations of this substance were administered to premature infants in the hope of stimulating the vital processes measured by survival. The results were encouraging.

### 33. CRANIOPHARYNGIOMA WITH INFANTILISM. CASE REPORT WITH CLINICAL AND PATHOLOGICAL STUDIES

Thomas H. McGavack, Raymond Harris, Andrea Saccone and Harry Goldberg, New York Medical College, Metropolitan Research Unit

Death of a man at age 54 with first symptoms at age 15, was preceded by five years continuous observation during which prolonged treatments included methyl testosterone, t-propionate, desoxycorticosterone acetate, alpha-estradiol dipropionate, desiccated thyroid and pituitary preparations, diets of known sodium, carbohydrate, protein and fat were used.

Post-mortem revealed a lack of normal anterior pituitary and the presence of a

calcified craniopharyngioma 4×4×3 cm. Organ weights in grams were thyroid and parathyroids 9.7; right testicle, 2.8; left testicle plus testosterone implant, 4.4; adrenals—right 3.6, left 3.3; prostate, 10.2; pancreas, 49.1; thymus unweighable.

Subjective improvements always followed testosterone therapy (25 mgs or more 3 times weekly) or desiccated thyroid (15–200 mgs daily) or a combination of these. Flat intra-venous glucose tolerance curves of untreated periods became normal under testosterone therapy but were not altered by other treatments; high cholesterol was reduced to normal by thyroid but unmodified by other medicants. Blood potassium was low, sodium high, with treatments of estradiol and desoxycorticosterone acetate. Fluid intake and urine output rose from 1.0 liter to 3.5 liters per day with desoxycorticosterone, 15 mgs daily, and a diet containing 2.6 gms sodium. Urinary creatine was decreased by t-propionate, increased by methyl testosterone, unchanged by other agents. Low insulin clearances were elevated by DCA and less by t-propionate. Capillary permeability was increased from minus 22% to plus 33% by DCA and less by estradiol; lowest values occurred with thyroid. Kepler-Robinson water tests similar to those in Addison's disease were not altered by treatment. Pituitary extract were ineffective in this patient.

#### 34. CONTINUOUS GROWTH OF NORMAL RATS RECEIVING PURE GROWTH HORMONE.

Herbert M. Evans, Miriam E. Simpson, and Choh Hao Li. Institute of Experimental Biology, University of California.

Normal, adult, plateaued, female rats (211 days old) have been injected 6 days weekly for 436 days with anterior hypophyseal growth hormone. The initial dose of 0.4 mg was gradually increased to 2 mg. Growth continued during the whole period, the experiment being terminated due to the advanced age of the animals. The greatest weight attained was 662 gm. The range of final weights in the experimental and control groups did not overlap; the smallest experimental rat weighed 410 g. the largest control 353 g. The average gain of 8 experimental rats was 293 g, of 5 controls 57 g. The average body length at autopsy of the experimental rats was 45.5 cm, of the controls 40.9 cm. Liver, kidneys, heart, stomach and intestine increased in weight in proportion to body weight. The thymus was not hypertrophied as occurs upon acute administration of growth hormone. The other endocrine organs were not increased in proportion to body weight, as might be anticipated from the absence of the specific hormonal stimulants in the growth hormone injected.

#### 36. OBSERVATIONS ON THE USE OF THE SERUM PHOSPHORUS LEVEL AS AN INDEX OF PITUITARY GROWTH HORMONE ACTIVITY; THE EFFECT OF ESTROGEN THERAPY IN ACROMEGALY.

Edward C. Reifenshtein, Jr., Laurence W. Kinsell,; and Fuller Albright. From the Department of Medicine of the Harvard Medical School and from the Medical Service of the Massachusetts General Hospital, Boston.

Three observations are presented in this paper: (1) The serum "inorganic" phosphorus level is elevated without a corresponding fall in the serum calcium level in most acromegalic patients; the same is true in growing children. (2) The high serum phosphorus level and many of the symptoms of acromegaly respond to estrogen therapy. Since it is known from the literature that the administration of estrogen alone inhibits growth in animals and that the simultaneous administration of growth hormone with estrogen prevents this inhibition, it is suggested that (other factors being equal) a high serum phosphorus level may be an index of pituitary growth hormone activity. (3) The negative calcium balance (a common finding in acromegaly) responds to estrogen therapy as does the calcium balance of post-menopausal osteoporosis. The evidence for the above observations and a discussion of certain implications, both academic and clinical, is given in this presentation.

36. FACTORS INFLUENCING THE PRODUCTION OF CARDIO-VASCULAR DISEASES BY ANTERIOR PITUITARY AND CORTICOID HORMONES.

Hans Selye. From The Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada.

Both desoxycorticosterone acetate (DCA) and lyophilized anterior pituitary tissue (LAP) produce malignant hypertension, nephrosclerosis, periarteritis nodosa of the cardiac vessels and myocarditis (with nodules resembling Aschoff's bodies) in the rat.

Unilateral nephrectomy and a high NaCl or a high protein intake sensitize the rat to these toxic effects of both DCA and LAP; "acidifying salts" (e.g.  $\text{NH}_4\text{Cl}$  or  $\text{CaCl}_2$ ) and low protein diets have an opposite effect.

Low protein diets also inhibit, and high protein diets enhance the ability of LAP to cause adrenal cortical hypertrophy.

In the adrenalectomized animal, none of the above-mentioned LAP overdosage manifestations are evident; hence, LAP probably acts because of its adrenotropic hormone content which causes the adrenal cortex to elaborate DCA-like corticoids.

In the case of DCA overdosage, the above-mentioned changes are accompanied by hypopotassemia, hypochloremia and periarteritis nodosa of the mesenteric vessels, while LAP treatment rarely produces these latter changes.

The cause of the slight qualitative differences between the actions of DCA and LAP have not as yet been elucidated. It is possible that the anterior pituitary produces substances which inhibit some of the actions of DCA, or that the natural (endogenous) corticoids liberated by the adrenal, under the influence of LAP, are qualitatively slightly different from DCA.

In rats sensitized by NaCl and unilateral nephrectomy, various types of non-specific damage (e.g. cold) produce lesions similar to those elicited by LAP or DCA. The theory is advanced that the spontaneous diseases of human pathology, which are imitated by LAP or DCA overdosage, are due to a defensive increase in the production of corticotropic and corticoid hormones. The above-mentioned cardio-vascular lesions could then be regarded as by-products of this adaptive defence reaction; that is, as "Diseases of Adaptation." (Subsidized by a grant of the Commonwealth Fund).

37. THE SUBSTANCE IN LATE PREGNANCY MARE SERUM CAUSING OVARIAN INHIBITION.

H. H. Cole. Division of Animal Husbandry, University of California, Davis.

In earlier studies, we (Cole and Hart, 1930) showed that, whereas the serum of mares in early stages of pregnancy contained large amounts of a gonadotrophin, in late pregnancy the serum inhibited ovarian activity in the immature rat. Furthermore, the ovaries of the mare in late pregnancy regress to a remarkable degree and are devoid of both corpora lutea and large follicles.

Because of the large amounts of gonadotrophin present in early pregnancy, the possibility existed that an antigonadotrophin was formed. Tests for antigonadotrophin were negative, however—a further substantiation of the concept enunciated by Leatham and Rakoff that gonadotrophins of homologous source are not antigenic.

Tests for lactogenic hormone, another substance producing ovarian inhibition, were likewise negative.

The evidence at hand indicates that the inhibition is due to estrogens present in the blood in low concentration. The inhibition produced by late pregnancy serum has been compared to that obtained with estradiol benzoate (Progynon B). In both instances, inhibition occurs if a dose is given equivalent to about one-fourth r.u. daily. Estrogens in the urine of pregnant mares produce a similar inhibition at comparable dosage levels.

The role which estrogens play in regulating gonadotrophic secretion will be discussed.

### 38. THE PROBLEM OF ANTIGONADOTROPINS IN CLINICAL THERAPY.

J. H. Leatham and A. E. Rakoff. From the Department of Zoology, Rutgers University, New Brunswick, and the Departments of Obstetrics and Gynecology and the Endocrine Laboratory, Jefferson Medical College and Hospital, Philadelphia.

Adequate clinical evidence is available to show that antagonists against equine gonadotropin and synapoidin (sheep pituitary and chorionic gonadotropin) develop in the serum during therapy. Antihormones persist for at least three months and with synapoidin the titres could be correlated with the response to therapy in cases of functional bleeding.

To establish a rationale for prolonged therapy, hormone specificity of antihormones was studied. Serum from patients treated for two to five months with synapoidin failed to reveal antagonists to synapoidin, equine gonadotropin, equine pituitary, chorionic gonadotropin or human pituitary with but one exception in which chorionic gonadotropin was inhibited. Patients who developed antihormones against synapoidin revealed that the antiserum would not antagonize the action of human pituitary but did inhibit equine gonadotropin and chorionic gonadotropin. The non-specific nature of the antiserum is indicated.

Two patients developed antihormones to equine gonadotropin but the serum did not antagonize the action of human pituitary or synapoidin. The antiserum formed against equine gonadotropin appears to be hormone specific.

Synapoidin and equine gonadotropin were administered to one patient at different times and the serum when tested was capable of inhibiting equine gonadotropin and chorionic gonadotropin but did not influence synapoidin.

### 39. END RESULTS OF TREATMENT OF PITUITARY DWARFS WITH CHORIONIC GONADOTROPIN AND SEX HORMONES.

W. O. Thompson, N. J. Heckel, and P. K. Thompson, Chicago.

Observations on the treatment of pituitary dwarfs during the last sixteen years warrant the following conclusions:

The only way in which growth can be accelerated in male pituitary dwarfs is by the administration of chorionic gonadotropin or male sex hormone. These materials insure that the growth component associated with puberty takes place and are therefore of value only if the gonadotropic-producing mechanism of the pituitary is deficient. They are in no sense a substitute for the thyroid hormone or for the growth factor of the pituitary. They influence growth by inducing puberty and causing the acceleration of growth and skeletal molding associated with puberty. The maximum acceleration of growth associated with the administration of these materials in the male pituitary dwarf is about 10 inches and the optimum time for starting the administration appears to be the eleventh or twelfth year.

In the female pituitary dwarf the administration of female sex hormone causes some acceleration of growth, although not as much as the male sex hormone in the male pituitary dwarf.

The thyroid hormone and various commercial preparations of the growth factor of the pituitary are not effective in stimulating growth in pituitary dwarfs.

Pituitary dwarfs treated with chorionic gonadotropin and the sex hormones remain short because they show only that increment of growth associated with puberty and there is no way at present of making up for the deficiency of pituitary growth factor.

### 40. ADVANTAGES OF MODIFIED PROTAMINE ZINC INSULIN IN THE REGULATION OF DIABETES.

Cyril M. MacBryde. Los Angeles.

A modification of protamine zinc insulin containing 0.5 mg. of protamine per 100 units (instead of the standard 1.2 mg.) has 25 per cent of the insulin content

in soluble, quickly-absorbed form, while 75 per cent is in the precipitate and is slowly absorbed over a period exceeding 24 hours. Maintenance therapy with this MPZ insulin has proved very satisfactory, direct comparative studies having shown better control with it than with insulin mixtures, globin insulin and other modified insulins.

The majority of patients needing 40 units or less of insulin daily can be well regulated with a single daily dose of standard PZ insulin. Of a series of 385 diabetic patients studied during a six year period, 233 (58 per cent) were well controlled with standard PZ insulin. The remaining 152 needed over 40 units daily and could not be regulated with standard PZ insulin, but 90 per cent of this group of severe diabetic patients were well controlled with MPZ insulin. Strength, energy and nutrition are better than with any other treatment program, and the incidence of complications has been reduced. Individual case studies of patients needing as much as 100 units daily illustrate the superiority of MPZ insulin, a more nearly normal 24 hour blood glucose curve being established with an undistorted diet and only one daily injection being required.

#### 41. EFFECT OF IODINE INTAKE ON THYROID IODINE DISTRIBUTION AND THYROID WEIGHT OF RATS TREATED WITH THIOURACIL AND OTHER GOITROGENS.

D. A. McGinty and E. A. Sharp. Research Laboratories, Parke, Davis & Company, Detroit.

Absorption of iodine (Rawson and collaborators, 1944) and formation of diiodotyrosine and thyroxine (Franklin and associates, 1944) by the thyroid of the rat is inhibited during thiouracil treatment provided iodine intake is at or near physiological requirements. If, under the same conditions, iodide is added to the drinking water in increasing concentrations, iodine accumulates in the thyroid gland in amounts proportional to increased intakes. Fractionation of thyroids from such animals by means of  $Zn(SO_4)_2$  and NaOH indicates, however, that practically all of the iodine exists in non-protein-bound form presumably as inorganic iodide. Since the iodine concentration in other organs under the same experimental conditions was much smaller, Salters suggestion (1945) that a loose combination of iodide and thyroid protein exists, is given support. Equivalent amounts of iodine as iodate or as diiodotyrosine also occur in  $Zn(OH)_2$  supernatants if given with thiouracil in the diet. In control experiments without thiouracil, added iodine caused an increase only in the protein-bound fraction of thyroid. The goitrogenic effect of thiouracil as well as that of certain other antithyroid substances studied, persists during high iodine intakes although some decrease in degree of thyroid hypertrophy was noted.

#### 42. THE REVERSIBLE INACTIVATION OF THYROTROPIC HORMONE. ITS INACTIVATION BY THYROID TISSUE AND REACTIVATION BY THIOURACIL AND OTHER GOITROGENIC AGENTS.

Rulon W. Rawson, Alexander Albert, Janet W. McArthur, Priscilla Merrill, Beatrice Lennan, and Charlotte Riddell. From the Thyroid Clinic of the Massachusetts General Hospital, Boston.

Explanted slices of normal rabbit thyroids were bathed in Tyrode's solution containing thyrotropic hormone at a temperature of 37°C. After a forty-eight hour period of incubation, the medium was removed and assayed. It was observed that exposure of 10 Junkmann Schoeller units of thyrotropic hormone to slices of one rabbit thyroid resulted in a complete loss of thyroid stimulating effect.

The inactivated hormone was treated with thiouracil and other goitrogenic drugs and assayed. After mixing or after incubation with these agents, the inactivated hormone was observed to recover in varying degrees its thyroid stimulating action. These agents in the amounts used to reactivate the inactive hormone when administered alone had no measurable effect on thyroids of the test animals.

Active hormone after incubation with these goitrogens was found to have a greater thyroid stimulating action than untreated active hormone. The same



augmentation was observed after the goiter producing agents had been removed by dialysis.

The theory is advanced that the action of certain goitrogens is at least twofold: that they interfere with thyroid hormone production and that in addition they augment the action of thyrotropic hormone.

43. SENSITIVITY OF THE REPRODUCTIVE SYSTEM OF HYPOPHYSECTOMIZED FORTY-DAY-OLD MALE RATS TO TESTOSTERONE PROPIONATE.

Miriam E. Simpson and Herbert M. Evans. Institute of Experimental Biology, University of California.

In a previous paper (Simpson, M. E., C. H. Li and H. M. Evans: *Endocrinology* 35: 96, 1944) it was reported that the testicular tubules of 40-day-old male rats were maintained and even caused to continue development during the 15 days following hypophysectomy when injected with extremely small doses of ICSH. Tubular stimulation, in fact, occurred at doses too low to prevent the accessory organs of reproduction from regressing to the hypophysectomized condition. As it has been assumed that ICSH acts indirectly through the male sex hormone produced, similarly prepared test animals were injected with varying doses of testosterone propionate to compare androgenic with gametogenic effects. This substance (in contrast with ICSH) proved equally good as a stimulant of testicular tubules and accessories. These findings do not sustain the explanation cited for the mode of action of ICSH on the testicular tubules.

44. THE SYNDROME OF CONGENITALLY ABSENT OVARIES, WITH INFANTILISM, HIGH URINARY GONADOTROPINS AND SHORT STATURE, WITH OTHER CONGENITAL ABNORMALITIES, SUCH AS SHORT WEBBED NECK, CUBITUS VALGUS, COARCTATION OF THE AORTA, ETC., AND TABULAR PRESENTATION OF TWENTY-ONE PREVIOUSLY UNPUBLISHED CASES.

H. Lissner, L. E. Curtis, Roberto F. Escamilla, and Minnie B. Goldberg. From the Division of Medicine, University of California Medical School, San Francisco, California.

About 50 cases of this syndrome have been published. We are adding 21 cases. The absence of ovaries has been demonstrated in 20 previously reported cases and in 4 of our patients, one of whom was only 13 years old. Urinary gonadotropins tested in 10 of our cases were abnormally high. Two of the remaining 11, however, were verified pathologically. The remaining 9 patients are characteristic clinically. Photographs are available for all but 2 of our 21 cases.

The absence of ovaries is considered responsible for the amenorrhea, absent mammary development, sparse sexual hair and high urinary gonadotropins—but not for the shortness. The latter may be the result of a germinal defect, like the ovarian agenesis and other congenital abnormalities. The shortness would be difficult to explain on a hormonal basis. For contrast, a photograph of a tall female, age 33, who was castrated at the age of 5, will be shown.

Early diagnosis is stressed so that measures to promote growth can be instituted, especially because the "bone-age" is usually only slightly retarded.

Estrogens are highly beneficial in causing breast development, growth of sexual hair, and, if given in cyclic fashion, regular withdrawal bleeding, with consequent profound improvement in morale.

45. ADRENAL ASCORBIC ACID RESPONSE TO ADRENOCORTICOTROPIC HORMONE IN INTACT AND HYPOPHYSECTOMIZED RATS.

Paul L. Munson and F. C. Koch. Biochemical Research Division, Armour and Company, Chicago.

Single subcutaneous injections of purified adrenocorticotrophic hormone (ACTH) into normal male rats decreased adrenal ascorbic acid concentrations one hour later as follows:

ACTH administered	No. of rats	Adrenal ascorbic acid: decrease from controls
gammas		per cent
2.5-5	36	3
10	29	8
20-25	40	18
40-50	34	20
80	30	22
100	11	42
160-400	32	39

Thirteen successive daily injections of purified ACTH into hypophysectomized male rats raised the ascorbic acid content of the adrenals as follows:

Daily dosage ACTH	No. of rats	Adrenal ascorbic acid
		gammas per rat
Saline only	63	27.4
40 gammas	67	38.2
200 gammas	68	43.7
0.8-1 mg.	28	52.1
Unoperated	13	85.0

When ACTH was administered at a level sufficiently high to increase the adrenal weight above that of unoperated controls the adrenal ascorbic acid of the treated group was still significantly less than that of the controls. Prolongation of the interval between last injection and autopsy from 24 to 48 hours did not change the values significantly.

Although we have demonstrated the existence of a quantitative relationship between ACTH dosage and adrenal ascorbic acid response both in intact and hypophysectomized rats, animal variation is high and the slope of the curve relating log-dosage and response is low. It is concluded that neither procedure will lead to an improvement over bioassay methods previously described. On the other hand, the recently introduced method of Sayers and Sayers (*Fed. Proc.* 5, 200 (1946)), using a single intravenous injection of ACTH in one-day hypophysectomized rats, has worked well in our hands, and we believe it shows promise.

#### 46. THE USE OF DESOXYCORTICOSTERONE ACETATE IN A BEESWAX MIXTURE FOR THE TREATMENT OF ADDISON'S DISEASE.

Charles F. Code, Edward H. Rynearson, and Marschelle H. Power. Section on Clinical Physiology, Division of Medicine, and Section on Clinical Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Beeswax mixtures have been used for the administration of histamine, heparin, penicillin and other substances in cases in which a delay in absorption is advantageous. In the treatment of Addison's disease, desoxycorticosterone acetate has been administered both in oil and as pellets. We have studied its injection in a beeswax mixture in fourteen cases. Three of the patients have died and their deaths will be discussed. Of the remaining eleven patients, two have had only one or two injections, six have had five to eight injections and three have had ten to twenty injections. The three patients who have had more than ten injections have now been treated for several years by this method. Their experience will be reported in detail.

#### 47. LUTEOTROPHIC ACTION OF CHORIONIC GONADOTROPHIN IN THE WOMAN.

W. E. Brown and J. T. Bradbury. Department of Obstetrics and Gynecology, State University of Iowa.

Two women were given chorionic gonadotrophin (Antuitrin-S) in doses of 20,000

i.v. per day. Treatment was started in the late luteal phase of the menstrual cycle and was continued until the onset of bleeding. Endometrial biopsies were obtained once a week, before, during and after treatment as a means of determining the sequence of changes in ovarian activity. The endometrium of these two women had gone through the normal sequence of changes since the last menstrual period and was a typically premenstrual secretory endometrium at the time of the initial injection. Menstruation was delayed 2 weeks beyond its expected date of onset in one patient, and was delayed 3 weeks in the second patient. The endometrial biopsies obtained during this interval of treatment were definitely secretory and had a marked decidual reaction (deciduoid??). The continued maintenance of this luteal endometrium indicates that the chorionic gonadotrophin has a definite luteotrophic action in the woman. The negative results in our earlier report Brown, Bradbury and Metzger (1941) were undoubtedly due to the low doses employed. These studies are being expanded and will be reported in detail.

#### 48. FURTHER OBSERVATIONS ON THE ABSORPTION OF SUBCUTANEOUSLY IMPLANTED PELLETS OF HORMONALLY ACTIVE STEROIDS.

Thomas H. McGavack and Herman Reinstein. N. Y. Medical College, Metropolitan Hospital Research Unit.

The rate of absorption of 75 mg. pellets of desoxycorticosterone acetate of constant surface area and hardness has been determined in 15 dogs and in 12 human beings. Similar studies have been made with 75 mg. pellets of testosterone and with 15 mg. pellets of estradiol benzoate in human beings. Experiences with pellets of testosterone implanted within the testicle of 2 human beings will also be detailed.

The over-all time for the absorption of the pellets of desoxycorticosterone acetate was between 10 and 12 months with an average daily absorption per pellet of 0.24 mg. The average period over which patients experienced symptoms was approximately 9 months.

Pellets of testosterone propionate were absorbed at the rate of approximately 0.3 mg. per pellet per day in both the dog and the human being, with an over-all absorption time of 8 to 9 months. Periods of symptomatic relief varied from 2 to 8 months.

Pellets of estradiol benzoate were absorbed at an average rate of about 0.05 mg. per pellet per day with a calculated over-all absorption time of approximately one year. Periods of subjective relief varied from 3 to 9 months.

About the area of testicular implant in one human being there was an active regeneration of testicular tissue. In the other no trace of seminiferous tubules could be found at autopsy some 3 months after a third implantation of 225 mg. of testosterone propionate.

It has been shown that 1.0 mg. desoxycorticosterone acetate absorbed daily from an implanted pellet is the equivalent in activity of approximately 5 mg. of the material in a sesame oil medium administered daily by subcutaneous injection. Approximately the same ratio holds for the implantations of testosterone propionate. Sufficient data have not been accumulated to determine the conversion equivalents of implanted pellets of estradiol benzoate in terms of periodic injections in an oil medium, but it has been possible to produce full estrogenic responses in the vaginal smear from a single 15 mg. pellet.

The number of pellets implanted has no relation to the rate of absorption of the individual pellet. Towards the end of the absorption period there is a decrease in the rate of assimilation, but this is not appreciable for the first five months after implantation. However, it seems unlikely that the decreased absorption is the only factor involved in the return of symptoms and signs of hormonal insufficiency prior to the end of the absorption period.

#### 49. ABSENCE OF RENOTROPIC ACTION OF PURE ADRENOCORTICOTROPIC HORMONE (ACTH).

Miriam E. Simpson, Choh Hao Li, and Herbert M. Evans. Institute of Experimental Biology, University of California.

Reiss has recently reported (Reiss, M.: *Nature (London)* 154: 737, 1944) in-

adrenocorticotrophic preparation. The conditions of his experiment have been duplicated as closely as possible in an effort to test whether electrophoretically homogeneous ACTH would have the same effect. It was not possible to show changes in renal histology or significant increases in the kidney weights.

#### 50 THE RATE OF METABOLISM OF STEROID HORMONES BY THE LIVERS OF DIFFERENT SPECIES

L. T. Samuels and C. J. McCauley, Department of Biological Chemistry, University of Utah, Salt Lake City

The rate of destruction of testosterone and estrone and estrogens has been studied after incubation with liver mince, using chemical methods of estimation. Liver tissue of the human, rat, mouse, rabbit and dog have been used. The rate of destruction is lowest in the human liver and the most rapid with rat and mouse livers. There appears to be no correlation between the rates of destruction of estrone and of testosterone. The bearing of these results on the reactions in different species will be discussed.

#### 51 THE COMPARATIVE EFFECT OF VARIOUS GOITROGENIC AGENTS ON THE COLLECTION OF RADIOACTIVE IODINE BY THE THYROID IN RATS AND CHICKS

Rulon W. Rawson, D. A. McGinty and Wendell Peacock. From the Thyroid Clinic of the Massachusetts General Hospital, Boston, the Research Laboratories of Parke Davis & Company, Detroit, and the Nuclear Physics Laboratories, Massachusetts Institute of Technology, Cambridge

The collection of radioactive iodine by the Thyroids of chicks and rats treated acutely and chronically with various goitrogenic compounds has been compared.

All of the agents studied were alike in preventing the collection of radioactive iodine administered one to six hours after a single injection of the various drugs. However, when administered chronically these agents differed radically in their effects. Thiouracil and related compounds blocked the collection of iodine in both rats and chicks. Amino mercaptothiazazole and phenylaminomethyl mercaptothiazoline blocked the collection of iodine in rats, but caused an increase in the collection of iodine in chicks. Potassium thiocyanate increased the collection of iodine in rats.

It is concluded that various goitrogenic agents produce their effects on the thyroid through different mechanisms and that the effects produced with such agents vary with the species.

#### 52 TURNER'S SYNDROME: A CASE REPORT

William M. Moffat, Santa Barbara

Since the syndrome of infantilism, congenital webbed neck and cubitus valgus in females was first described by Henry H. Turner in 1938 based upon a collection of 10 cases, only 6 cases presenting the entire triad have been published.

This report describes the case of a 21 year old girl of above average intelligence. She is 62½ inches in height. She has a web of skin extending from behind each ear to the shoulder. The posterior surfaces of these webs are covered with thick hair. She has cubitus valgus. The external genitalia are undeveloped, no uterus is palpable and the cervix is about 5 mm. in diameter. No glandular tissue can be felt in her breasts which are rudimentary with small areolae and no nipples. Her hips are flat like a boy's. Her skin displays many pigmented moles. Vaginal smears show that the mucosal cells are completely lacking in glycogen. X-ray studies show an epiphyseal development of 16 years of age. The relationship of Turner's Syndrome to other reported syndromes presenting some of the same features is discussed.

#### 53 INFLUENCE OF METABOLISM ON ENURESIS

Robert M. Oslund, Ross-Loos Medical Group, Los Angeles

Nocturnal enuresis appears to be a functional disturbance resulting from or accompanying low metabolism.

Patients ranging in age from 3½ to 19 years, studied for abnormal physiological bone age, were not indicative. Basal metabolic readings were usually only slightly

below normal; however, thyroid given to these patients produced cessation of nocturnal enuresis within two to three weeks; similar results although not as rapid, may be obtained from pituitary material.

As a great many hypothyroid patients do not experience nocturnal enuresis, the results are therefore interpreted as purely metabolic and not a thyroid deficiency.

54. QUANTITATIVE INHIBITION OF OESTROGEN EFFECT ON CHICK OVIDUCT BY PROGESTERONE.

Roy Hertz. National Institute of Health, Bethesda, Md.

Inhibition of estrogen-induced weight increase in the chick oviduct by simultaneously administered progesterone is proportional to the progesterone dosage up to a maximum, beyond which even a six-fold increment in progesterone level effects no further inhibition. In the presence of a maximally effective progesterone dosage a sixteen-fold increase in estrogen dosage does not overcome the progesterone inhibition. Preliminary administration of maximally effective doses of progesterone for two days prior to the initiation of estrogen treatment does not enhance the degree of inhibition obtained.

Homogenates of the oviduct from chicks treated with an inhibitory combination of estrogen and progesterone are without effect upon the estrogen response in the chick. Additional studies on the mechanism of the estrogen-progesterone antagonism will be reported.

55. THE EFFECT OF SUBCUTANEOUS ADMINISTRATION AND TOPICAL APPLICATION OF STEROID PREPARATIONS TO THE PIGMENTATION AREA OF THE HAMSTER.

Herbert S. Kupperman. Department of Endocrinology, University of Georgia School of Medicine, Augusta.

In the costo-vertebral area of the golden hamster an area of excessive melanin deposition has been observed in the adult male hamster. This area is about 0.5 cm. in diameter, also associated with an increased amount of coarseness of the peltage. Pigmentation is absent or diminished in immature and adult females, immature and castrated males, and is of decreased intensity in senile males. Pigmentation and coarseness of the tuft of hair may be induced by topical application or subcutaneous administration of androgenic preparations. Estrogen, progesterone and desoxycorticosterone have a suppressing effect on the pigmented area. Simultaneous administration of androgen and estrogen to castrated males produces essentially the same effect as androgens alone, thus failing to demonstrate antagonism between folliculoid and android hormones. The relative effectiveness of the steroid preparation in producing pigmentation in the castrated male or female is closely correlated with the android activity of the preparation. The topical application of alcoholic solution of male hormone as a means of assay for android activity is discussed.

56. THE INFLUENCE OF THE ADRENAL CORTEX ON THE METABOLISM OF THE EVISCERATED RAT.

Sidney Roberts. From the Worcester Foundation for Experimental Biology, Shrewsbury.

Adrenalectomy following evisceration in the fasted rat produced a 50 percent reduction in survival time and an increased rate of blood sugar disappearance. Upjohn cortical extract in oil had a small moderating effect. Other extracts tested were still less active. Since estrogens have been found to be inactive under similar circumstances (Szego & Roberts, *Endocrinology* 36: 104, 1945), the viscera may be essential for the complete activity of steroid hormones in general.

Adrenalectomy in the eviscerated rat did not influence:

- (1) rate of rise of blood amino acids,
- (2) rate of fall of blood volume,
- (3) simultaneous renal arterio-venous (A-V) differences for sugar, amino acids, and hemoglobin.

Simultaneous analyses of tail and aortal blood samples for sugar revealed that

adrenalectomy uniformly produced an increased peripheral A-V difference. This might be due to more rapid sugar utilization. Other considerations, however, indicate that the primary effect of adrenalectomy in the eviscerated rat is hemodynamic, and that the increased peripheral A-V difference reflects an increased circulation time. The circulatory changes include a reduction in renal blood flow, which suggests that the actual rate of gluconeogenesis in the kidney is reduced by adrenalectomy even though renal A-V differences for sugar are unchanged.

#### 57. THE NATURE OF BENADRYL ACTIVITY: GLUCOSE TOLERANCE CURVES.

Herman Reinstein and T. H. McGavack.

N. Y. Medical College, Metropolitan Hospital Research Unit.

Intravenous glucose tolerance curves have been performed by standard techniques on 17 subjects ranging in age from 21-71 years. Each patient was maintained on a diet of 2300 calories, containing 200 gm. of carbohydrate, 95 gm. of protein, and 125 gm. of fat, for 3 days before the performance of the first glucose tolerance test and throughout the entire period of study except on the days during which tests were taken. Three tests were done on each subject: one without Benadryl (Curve I), one beginning one-half hour following the ingestion of 400 mgm. of Benadryl orally (Curve II), and the third, one-half hour following the administration of 30 mgm. of Benadryl intravenously (Curve III). The results of each of the three tests have been averaged for the 14 patients. In each instant a composite curve was drawn; the first and second of these composite curves closely approximate each other. However, it was noted that in younger individuals the area of the curve obtained following Benadryl orally was significantly larger than that of the control, whereas in older individuals, above 50, the reverse was true. Following the use of Benadryl intravenously (Curve III) there was a significant increase in sugar tolerance in all subjects irrespective of age, as shown by a decrease in the areas of the individual and composite curves respectively. In order to rule out any normal variation in glucose tolerance when determined at three day intervals, three subjects were given the same regime as the 14 test subjects mentioned above except that no medication was used in conjunction with any of the three tests obtained per subject. It is significant that in each of these three subjects curves of smallest area were obtained in the first test with a moderate but significant increase in the area with each of the two succeeding examinations.

These findings will be discussed in relation to the nature of the action of Benadryl and its antihistamine effects.

#### 58. NATURE AND DISTRIBUTION OF THE SKELETAL ABNORMALITIES IN CUSHING'S SYNDROME.

Fuller Albright, Anne P. Forbes, and Edward C. Reifenstein, Jr. Dept. of Medicine, Harvard Medical School and Massachusetts General Hospital, Boston.

It is pointed out that the demineralization of the bone in Cushing's Syndrome is the result of osteoporosis. By "osteoporosis" is meant that bone condition where the primary abnormality is a failure of the osteoblasts to lay down matrix.

The osteoporosis in Cushing's Syndrome has a marked predilection for the spine and pelvis. A case of Cushing's Syndrome in a girl of thirteen is presented. The x-rays of the bone before and after the condition was alleviated are most instructive.

The effect of potassium on the calcium balance of two cases of Cushing's Syndrome are presented.

#### 59. MANAGEMENT OF THREATENED AND HABITUAL ABORTION BY LARGE DOSES OF ORAL ESTROGEN.

A. R. Abarbanel. Department of Obstetrics and Gynecology College of Medical Evangelists, Los Angeles.

Fifty cases of threatened and habitual abortion were treated by means of oral estrogen (diethylstilbestrol) in doses ranging from 15 to 500 mg. daily. The homeostatic effect was evident in 4 to 24 hours.

A large percentage of fetuses were salvaged. It is felt that the effect of estrogen

upon the endometrial vascular bed, particularly at the site of placentaion, is responsible for the favorable clinical results.

60. CLINICAL SYNDROMES OF ABERRATIONS IN CORPUS LUTEUM FUNCTION.

Virgil O. Parret and A. R. Abarbanel. From Department of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.

The following syndromes which are felt to stem from aberrations of corpus luteum function are briefly presented and correlated with the pathological findings:

Hemorrhage into corpus luteum (simulating an acute surgical abdomen).

Persistent corpus luteum simulating ectopic pregnancy.

Lutein cysts resembling chocolate cysts of endometriosis.

Persistent corpus luteum causing prolonged amenorrhea of several years.

Luteinized thecoma and also luteoma causing masculinization syndrome.

61. PROBLEM OF "CLOSED FALLOPIAN TUBES" HORMONAL DIFFERENTIATION OF TUBES CLOSED BY SPASM FROM THOSE CLOSED BY ORGANIC PATHOLOGY BY MEANS OF METHYL TESTOSTERONE.

A. R. Abarbanel. Department of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.

Twelve patients, who were diagnosed as having "closed tubes" and advised that they were now sterile, were given oral methyl testosterone, 5 mg. sublingually per day for one to three months. In each case the tubes were then found to be patent. In four cases pregnancy ensued during therapy.

The modus operandi is discussed.

62. THE USE OF SODIUM PARA-AMINO BENZOATE PARENTERALLY IN THE TREATMENT OF HYPERTHYROIDISM.

Louis Berman, N. Y. City.

In a preliminary communication to the Society for Experimental Biology and Medicine in May, 1945, a report was presented of beneficial therapeutic effects obtained in six ambulatory cases of hyperthyroidism by the parenteral administration of one gram or larger doses of the sodium salt of para-aminobenzoic acid six times weekly over a period of months with no unfavorable by-effects such as have been reported by clinicians employing thiourea and thiouracil. Eight more cases of hyperthyroidism so treated will be reported.

The treatment of the first case was begun in 1943, a patient with hyperthyroidism complicated with vitiligo to whom the sodium salt was administered as an attempt to influence the skin pigmentation disturbance. The oral use of para-aminobenzoic acid by itself and as a supplement to the parenteral administration of its sodium salt will also be discussed. Observations of the effects on pulse, blood pressure, weight, basal metabolism, blood cholesterol and the clinical symptoms and course of the disease will be presented. The details of the eight other cases will be given in addition to further observations on the six originally treated and followed up.

63. HYPOGONADOTROPHIC ENUCHOIDISM—ITS CLINICAL AND LABORATORY DELINEATION FROM OTHER FORMS OF HYPOGONADISM WITH A DISCOURSE ON TREATMENT.

Carl G. Heller and Warren O. Nelson. Departments of Physiology and Medicine, University of Oregon Medical School, Portland, and Department of Anatomy, University of Iowa, Iowa City.

Gonadotrophic hormone assays and testicular biopsies were found to be the most reliable laboratory criteria for establishing the diagnosis of hypogonadotrophic eunuchoidism. After laboratory classification it was possible to delineate this group from other forms of eunuchoidism by clinical means and by use of a therapeutic test.

Successful correction occurred following administration of chorionic gonadotrophin and a purified follicle stimulating hormone (prepared by McShan). Response was judged by clinical improvement and laboratory and serial biopsy changes.

# 64 DETERMINATION OF CORTICOSTEROIDS IN URINE

B L Lowenstein, A C Corcoran, and Irvine H Page From the Research Division of the Cleveland Clinic Foundation, Cleveland Ohio

The present method is based on periodate oxidation (Fieser Fields and Lieberman) of the primary alcohol group at C<sub>1</sub> which yields one mol of formaldehyde per mol of corticosteroid oxidized. Formaldehyde is then determined by the method of MacFadyen

Procedure To a 3 cc aqueous aliquot of a urinary extract (Venning, Hoffman and Browne) is added 0.1 cc of 0.05 M HIO<sub>4</sub> in 0.3 N H<sub>2</sub>SO<sub>4</sub>. Oxidation proceeds at about 25°C for 20 minutes when it is arrested by addition of 0.1 cc of 6 per cent SnCl<sub>2</sub>. Five cc of 0.2 per cent chromotropic acid (Eastman) in 15 M H<sub>2</sub>SO<sub>4</sub> are added and the mixture heated for 30 minutes at 100°C. The cooled solution is made up to 12.5 cc by addition of 9 M H<sub>2</sub>SO<sub>4</sub> and color density read in the Coleman Model 6 spectrophotometer

The method gives good recoveries from urine samples containing added cortical extract. The average excretion of corticosteroids in normal males is 5-8 mg per 24 hours, expressed as dehydrocorticosterone. In a case of Addison's disease, the value was 0.15 mg and in one of Cushing's syndrome, 21 mg per 24 hours

The advantages of the method lie in simplicity, lack of urinary "blank" and in that the estimates include both active and partially reduced corticosteroids

# 65 THE EFFECT OF HYPOPHYSECTOMY ON THE TIME OF LAY OF THE HEN'S EGG

Irving Rothchild (Introduced by Richard M Fraps) U S Department of Agriculture, Agricultural Research Center, Beltsville, Maryland

Delays in lay occurred in Rhode Island Reds and White Leghorns, after either complete or partial hypophysectomy performed either on the day of ovulation or on the day of expected lay, no delays however, occurred after sham hypophysectomy. The distribution of results according to breed, completeness of operation, and time of operation was as follows

	Rhode Island Reds	White Leghorns
Complete hypophysectomy on day of ovulation	delays in 12 out of 25 birds	delays in 9 out of 27 birds
Complete hypophysectomy on day of expected lay	delays in 4 out of 9 birds	delays in 1 out of 10 birds
Partial hypophysectomy on day of ovulation	delays in 8 out of 20 birds	delays in 1 out of 7 birds
Partial hypophysectomy on day of expected lay	delays in 2 out of 5 birds	delays in 2 out of 3 birds
Sham hypophysectomy on day of ovulation	no delays in 16 birds	no delays in 15 birds
Sham hypophysectomy on day of expected lay	no delays in 4 birds	

These data indicate that removal of or injury to the AP results in partial interference with the determination of the time of normal lay. The nature of AP participation in the process of lay is under further investigation

# 66 PARATHYROIDITIS SYNDROME IN PITUITARY BASOPHILISM

Robert M Perlman San Francisco

Pathologic bone changes are an almost invariable accompaniment of pituitary basophilism. In earlier papers discussion centered around the probability that such changes are the result of a "primary" pituitary malady which secondarily affects the parathyroid glands, upsetting the calcium metabolism and thereby leading to disturbances in bone structure. It was shown that an intricate parathyroid-pituitary relationship also occurred in pituitary eosinophilism, resulting in a definite symptom complex which was later described as the "Parathyroid-pituitary Syndrome in Pituitary Eosinophilism". Altogether special mechanisms must enter into play when basophilic hyperpituitarism occurs simultaneously with hyperparathyroidism. Such mechanisms must be investigated separately and interpreted clearly, hence, *raison d'être* for this present paper



Substantial evidence is presented in the body of this paper to indicate that the basophilic version of the parathyropituitary syndrome may find expression in either of two extreme or a multitude of intermediate forms: 1) Cushing's syndrome in its banal form, with relatively mild skeletal destruction ("osteoporosis and osteomalacia" leading to scoliosis, kyphoscoliosis, lordosis, etc.). 2) Cushing's syndrome complicated by an accentuated osteoclastic skeletal resorption and fibrous neoformation of osseous tissues. These processes can become intense enough to render the full-fledged, typical, clinical and anatomical picture of von Recklinghausen's bone disease complete with spontaneous fractures and adenomatous parathyroid hyperplasia. The Syndrome may express itself in varying degrees, and may be complicated further by the intervention of renal pathology.

#### 67. DIURNAL VARIATIONS IN THE LEVELS OF BLOOD GLUCOSE OF NORMAL HUMAN BEINGS SUBJECTED TO VARIOUS TYPES OF CALORIC RESTRICTION.

David Schwimmer and Thomas H. McGavack. N. Y. Medical College, Metropolitan Hospital Research Unit.

Fifty-seven subjects have been divided into groups and given varying amounts of carbohydrate, protein, and fat with total caloric equivalents ranging from 900-1800 calories. The protein of the diet varied from 0-10% by weight. The subjects were fed at 9 A.M., 1 P.M., 5 P.M., and 9 P.M., with divisions of  $\frac{1}{2}$ ,  $\frac{1}{3}$ ,  $\frac{1}{4}$  and  $\frac{1}{5}$ , respectively. The widest fluctuations in blood glucose were observed in subjects who received diets containing only carbohydrate and fat. This was true irrespective of what caloric equivalent was used. Many of the subjects on these diets showed hypoglycemic symptoms and the signs came on as a rule between one-half and two hours after the 1 P.M. feeding. Simultaneously, levels for blood sugar dropped to levels as low as 50 mgm. per 100 cc. Sources of protein supplements were malted milk, lactalbumin, and dried egg white. The amino-acid methionine was similarly tried in lieu of and with protein. Methionine alone had no significant influence on the blood sugar trend. All forms of protein decreased the range of variation in the levels for the glucose of the blood.

When the above findings were brought into relation with data simultaneously procured regarding urinary volume, solutes, nitrogen balance, electrolyte balance and so forth, it was concluded that protein may serve a very useful purpose as a part of restricted rations.

#### 68. THE ROLE OF SEX HORMONES IN THE ORIGIN AND DEVELOPMENT OF ENDOMETRIAL GLANDS IN THE OPOSSUM.

Carl R. Moore and Elizabeth A. Failor. Hull Zoological Laboratory, The University of Chicago.

In the young opossum uterine development is slow hence is excellent for the determination of sex hormonal influences. Muellerian ducts are formed between postnatal days 3 and 10; oviducts, uterus and lateral vaginal canals are distinguishable by day 30. Uterine growth and differentiation continue progressively and by day 80 the smooth epithelial lining changes to low villi and shallow crypts. Endometrial glands arise as balls of cells from base of crypts about days 85-95 and hollow out into small flask-shaped glands by day 100. Rapid gland formation and elongation characterize postnatal days 100-140.

Bilateral ovariectomy on day 20 fails to delay uterine differentiation up to the time of usual gland formation (days 85-95) but it does prevent gland formation. Ovariectomy from days 80 to 95 causes a cessation of gland development even when glands are in process of development at operation.

Androgens as well as estrogens stimulate endometrial gland formation precociously as early as day 40 but sensitivity of the uterus to respond increases as the time of gland formation is approached.

It becomes clear that 1) endometrial gland formation and development is a function of estrogenic hormones from the ovary; 2) this is not an estrogen specific response but occurs with androgens; 3) the earliest detectable ovarian secretion occurs around days 85-95; 4) early uterine differentiation does not depend upon secretions from the developing ovary.

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## THE SOURCE OF EXCESS CREATINE FOLLOWING METHYL TESTOSTERONE<sup>1</sup>

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### INTRODUCTION

SINCE among the steroids only the 17-methylated compounds cause increased formation of creatine, the present studies were designed to give some information regarding the site of this action. Wilkins and Fleishmann (11) in 1941 first described the production of creatinuria in undeveloped dwarfs who were treated with methyl testosterone. Like testosterone, this compound caused increased nitrogen storage and growth, but whereas testosterone administration led to a small decrease in creatine output, methyl testosterone caused a marked increase in creatine excretion after a latent period of six to sixteen days.

Samuels, Henschel and Keys (8) in 1942 described this increased creatinuria after administration of methyl testosterone to normal young men. The output rose to as high as one gram per day in certain individuals. Not only was there a creatinuria but the blood creatine levels increased. These workers, therefore, came to the conclusion that the creatinuria was due to an increased formation of creatine rather than any change in the renal threshold.

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In recent work Wilkins and Fleischmann (12) found that only methylated derivatives of the androstane nucleus were effective. Methyl testosterone, methyl androstanediol-3,17 and methyl androstene- $\Delta_5$ -diol-3,17 all caused creatinuria, but ethyl testosterone was ineffective. A number of other non-methylated steroids were also found to be inactive. This work indicated that the active steroids might be associated with the methylation involved in creatine formation. It was pointed out by Wilkins and Fleischmann, however, that the amount of creatine produced would require many more methyl groups than the methyl testosterone could supply. The idea has, therefore, been advanced that methylated steroids may act as catalysts or transfer substances for methyl groups in the methylation process.

In the work of Wilkins and Fleischmann a delay has been noted in the appearance of creatine in the urine, varying from six to sixteen days after administration. The level then rises rapidly for the first 24 days and continues its upward trend for about four months after which the creatine output is maintained at a fairly constant level. Upon cessation of methyl testosterone administration, according to Wilkins and Fleischmann, there is a rise in creatine excretion for a short time followed by a rapid return to the level which existed before treatment.

Thus far, no animal other than the human being has been found which will show increased creatine excretion after administration of methyl testosterone. Dogs, rabbits, guinea pigs, rats and pigs have been tested with no effect. In our own laboratory we have failed to obtain creatinuria in either monkeys or rats. In the case of the rats, plasma and tissues have shown no evidence of any change in creatine levels. It is, therefore, necessary to use human beings in any study of creatine formation after methyl testosterone administration.

In determining the site of formation, therefore, it was necessary to select patients in which the organs most likely to be involved were sufficiently damaged to impair function seriously. Borsook and Dubnoff (3, 5) found that glycocyamine was produced by kidney tissue, and that this compound accelerated the formation of creatine by liver slices. They, therefore, advanced the hypothesis that glycocyamine is formed in the kidneys from glycine and arginine and is transported to the liver where it is methylated by methionine or other methyl donators.

The chemical cycle has been confirmed by experiments by Bloch and Schoenheimer (2), but the anatomical localization has been questioned by other workers. In fact, Borsook and Dubnoff (4) observed that creatine was formed in the kidney of mammals, but its formation was not accelerated by the addition of glycocyamine or methionine. It is possible, therefore, that the kidney as well as the liver is involved in creatine

synthesis. The precursors in the latter case either would not seem to be those postulated for the liver, or glycocyamine and methionine are supplied at an optimum rate by the kidney tissue.

We have, accordingly, studied cases of hepatic and renal disease in an effort to localize the action of methyl testosterone. Since renal function and water balance are disturbed in these conditions it was necessary to study blood levels as well as urine excretion.

### METHODS

Subjects for the study were selected from the wards of the University of Minnesota hospitals and the Salt Lake County General Hospital. They were placed on a low creatine diet. Forty-eight hours later the first of three consecutive twenty-four hour urine collections was begun. These collections were made from morning to morning. At the end of each twenty-four hour collection a sample of blood was drawn. At the end of the collection period the patients were returned to the regular diet of the hospital until forty-eight hours before collection of the next sample when the low creatine diet was again resumed.

After collection of the first three urine and blood samples administration of methyl testosterone was begun. In most cases a 10 mg. tablet was taken before each meal and two before retiring, making a total of 50 mg. per day. In some cases two 10 mg. tablets were taken before each meal, thus making a dose of 60 mg. per day. A series of three consecutive urine and blood samples was collected beginning on the 9th and 19th days. In some normal cases the drug was continued for 28 days and samples were collected at the end of that time and at ten day intervals after cessation of the drug.

The plasma and urine were analyzed for preformed and total creatinine (7). The only change was to lengthen the autoclave period to forty-five minutes after it had been demonstrated that the conversion of creatine to creatinine was not complete in the time originally given. The values from each set of three consecutive samples were averaged to give the levels recorded in the graphs and tables.

### RESULTS

#### Studies of normal subjects

The plasma and urine levels of creatine in normal women and men before, during, and after methyl testosterone administration are given in Figure 1. All of these subjects were on a low creatine diet for forty-eight hours before and during the collection of samples. In all cases no significant increase in urine creatine was observed at the end of the first ten days of treatment, but was present at the end of twenty days. On the other hand there was a small rise in plasma levels in all except two cases at

the end of ten days. The rise at the end of twenty days, however, was considerably greater.

Figure 2 illustrates the effect of oral creatine on creatinemia following methyl testosterone. If normal men consumed an ordinary meat and vegetable diet throughout the treatment period there was only a small increase in plasma levels at the end of five days but a marked one at the end of twelve days. If one gram of creatine was administered in addition to the

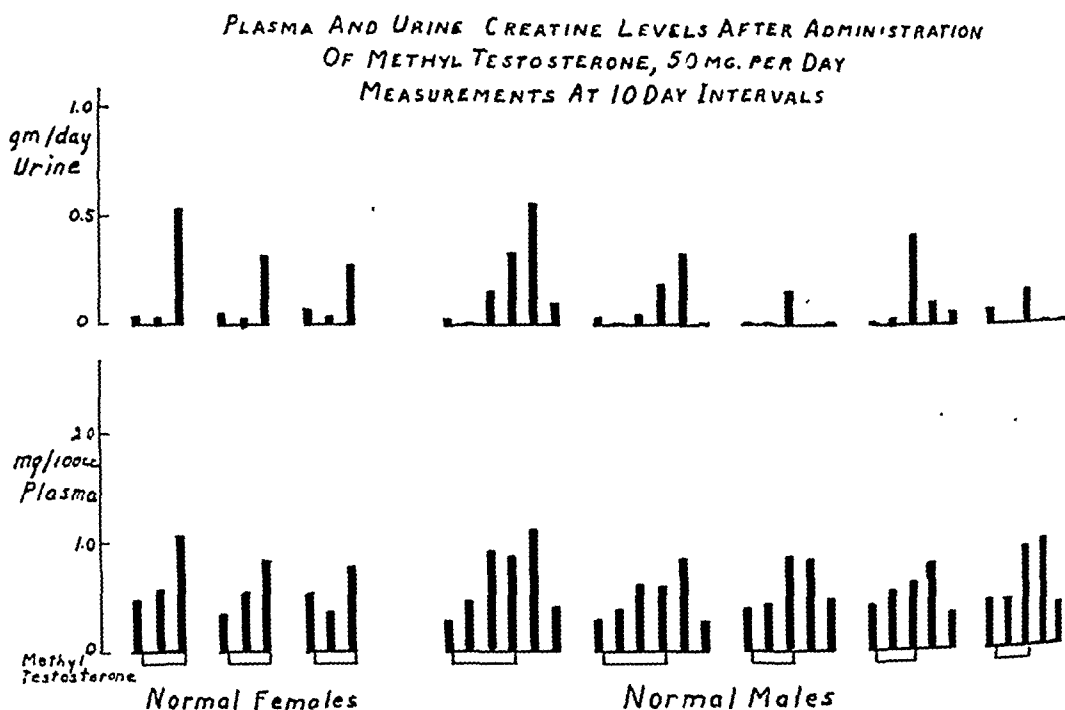


FIG. 1

normal diet the plasma level, although the same without administration of methyl testosterone as in the low creatine and ordinary diet groups, showed a marked rise within five days after administration of the steroid, and continued to rise. Apparently the greater the intake of creatine the more promptly a significant rise occurs in the plasma and in the excretion of creatine. This would indicate that methyl testosterone probably accelerates creatine formation soon after its initial administration. The excess creatine which is formed passes into the tissues where a concentration 30 to 400 times that found in the plasma exists. There is a limit, however, to the amount of creatine which the tissues can take up at this ratio. When this is exceeded, the creatine level of the blood rises rapidly until at values between 0.6 and 0.7 mg. per 100 cc. of plasma the creatine threshold is exceeded and creatinuria develops.

## Studies on hepatic and renal disease

Figure 3 shows the plasma levels and urinary excretion of creatine in cases of hepatic and renal disease. In a number of other cases urine levels alone were studied but since urine levels do not reflect blood levels accurately in the presence of severe glomerular damage as seen in *Cases 5, 7 and 8*, we have not included them in the tabulation.

Hepatic disease, even when terminal, did not interfere with the rise in

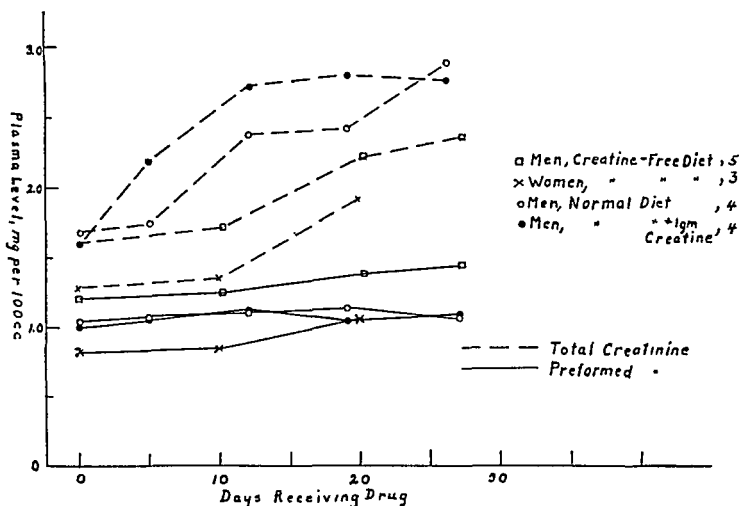


FIG. 2. Change in plasma creatine concentration during administration of 50 mg. methyl testosterone in groups with varying intakes of creatine by mouth. Averages of number of subjects indicated.

creatinine output produced by methyl testosterone. Two cases of cirrhosis died while under treatment with the drug, but showed a rapid increase in creatinemia and creatinuria up to the time of death. In the one case of cirrhosis and one of fatty degeneration (these patients lived for a short period of time after tests were run), the creatine levels decreased after cessation of therapy with the drug. It seems, therefore, that if the liver is involved in the increased formation of creatine after administration of methyl testosterone, it is able to carry on this function adequately when its other functions are impaired to an extent incompatible with life.

In the cases of nephrosis studied there also was ample evidence of the

influence of methyl testosterone on creatine formation. Since in these cases the creatine levels in the blood were already somewhat elevated, the rise in plasma creatine was rapid from the beginning of treatment. Creatinuria was not so marked because of the general renal failure. It seems that the renal and hepatic damage in nephrosis, even when severe, does not prevent the action of the methylated steroids.

In the milder cases of nephritis the same situation was found. There was an immediate rise in the plasma creatine levels which was not always

PLASMA AND URINE CREATINE LEVELS FOLLOWING ADMINISTRATION  
OF METHYL TESTOSTERONE, 50 MG. PER DAY  
MEASUREMENTS AT 10 DAY INTERVALS

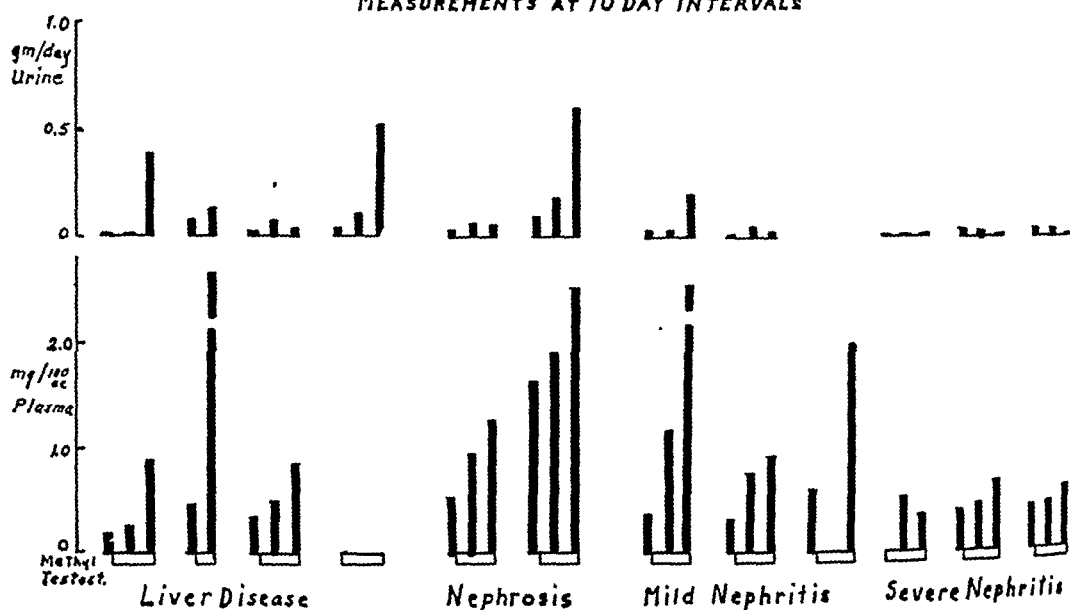


FIG. 3

reflected in urine creatine. This was not a true rise in the creatine threshold, since it probably did not represent increased absorption; instead, it represented decreased filtration.

The only condition in which there was a significant influence on creatine formation was severe nephritis. Here there was no significant rise in the plasma creatine level nor in the creatine output in the urine. There would appear to be a slight increase in the plasma creatine levels in two of the three cases illustrated in Figure 3. A study of Table 1 in which the ratio of total creatinine (creatinine plus creatinine) to preformed creatinine is given will show that there was no significant rise in this ratio in these cases. The slight rise in plasma creatine was not due to an increased production of creatine but to the decrease in glomerular filtration which consequently backed up both creatinine and creatine in the blood.

## DISCUSSION

The data presented here are in accord with the data of Bloch and Schoenheimer (1) that creatine from any source enters into the general creatine metabolism of the body; there was no distinction between plasma creatine due to normal endogenous metabolism, creatine produced after methyl testosterone administration, and that ingested.

TABLE 1. RATIO OF TOTAL TO PREFORMED CREATININE IN BLOOD AND URINE OF SUBJECTS TREATED FOR 20 DAYS WITH METHYL TESTOSTERONE, 50 MG. PER DAY

	Sex	Untreated		Treated 10 days		Treated 20 days	
		Blood	Urine	Blood	Urine	Blood	Urine
8 Normal	M	1 23-1 54	0 99-1 05	1 34-1 41	0 99-1 14	1 39-1 82	1.01-1 28*
		1 34	1 02	1 37	1 03	1 61*	1 08
3 Normal	F	1 42-1 71	1 02-1 06	1 46-1 67	1 01-1 03	1 73-1 99	1 22-1 33
		1 57	1 04	1 58	1 02	1 80*	1 26*
L J Hypopit	M		1 20*	2 14*	1 52*	2 18*	1 68*
S Z Cirrhosis	M	1 29	1 02	1 45*	1 05	1 81*	1 94
P B Cirrhosis	M	1 32	1 03	1 33	1 00	3 24*	1 79*
J Y Fatty Liver	F	1 14	1 06	2 17*	1 18*		
A R. Cirrhosis	F		1 08		1 16*		2 24*
G R Nephrosis	M	1 66*	1 52*	1 91*	2 06*	2 51*	3 09*
A P Nephrosis	M	1 30	1 05	1 52*	1 06	1 59*	1 06
J P Nephrosis	M	1 31	1 03	1 74*			
W M Nephrosis	M		1 05		1 34*		
Mild							
S G Chr Nephritis	F	1 14	1 05	1 32	1 04	1 70*	1 31*
M B Chr Nephritis	M	1 33	1 00	1 83*	1 04	1 81*	1 00
D D Chr Nephritis	M		1 03		1 76*		
Severe							
D H Chr Nephritis	M		1 01	1 23	1 01	1 28	1 03
M R Acute Nephritis	F	1 22	1 04	1 23	1 04	1 30	1 03
H P Acute Nephritis	M	1 35	1 04	1 35	0 99	1 49	1 03

\* Indicates a significant increase above normal

The course of events observed can best be explained by the assumption that creatine from any of these sources first is distributed between cells and circulating fluids at the high ratio seen under ordinary conditions. On this basis an excess production of 0.5 gm. a day could be accumulated for six days or more before the general increase in the tissues would equal ten per cent of the original concentration.

The increased concentration would then increase conversion to crea-



tinine and account for the smaller but significant increase in this component in the plasma and urine. Here again creatine from any source appears effective.

Apparently the ability to increase tissue concentrations, and perhaps also destruction, at this high ratio is soon reached, however, and as creatine production continues to increase the distribution-ratio rapidly approaches that of any solute acting under purely osmotic forces. Thus if the tissues have been saturated either because plasma levels have risen due to reduced filtration or because of ingestion the administration of methyl testosterone brings a prompt marked rise in plasma creatine levels. On the other hand, in the normal individual, the rise in plasma creatine is slow at first, but rises at an accelerated pace as treatment continues.

Our results also confirm the observations of Tierney and Peters (10) regarding the level of the renal threshold in men. In any case, except those with renal damage, whenever the plasma level exceeded 0.6 to 0.65 mg./100 cc., significant creatinuria occurred. Our observations on women, however, are not in agreement. Tierney and Peters found that orally administered creatine increased the plasma creatine levels more markedly and caused more creatinuria in women than in men. He assumed that the tissue capacity was already reached in the former sex. If this were the case in our normal female subjects, we should have expected an earlier rise in plasma and urine creatine levels than in men. This was not the case. This may be because of the limited number. None of the young women showed any significant creatinuria before administration of the drug.

It would seem that methyl testosterone action involves the kidney and requires little, if any, functioning liver tissue; otherwise one would have expected liver damage to have interfered more with creatine formation. Certainly the failure in creatine formation after renal damage supports this, although as an isolated fact this last observation would simply indicate that the kidney was involved in the formation of creatine or of its precursors. The structure of the glomerulus and the renal arginase (9) activity is markedly affected by methyl testosterone and testosterone (6), and it may well be that they also increase the enzymes involved in renal creatine synthesis; only the methylated steroid, however, will supply the methyl groups required.

There remains the possibility that creatine formation after administration of the steroid occurs in some other tissue, such as the muscle, but requires a precursor such as glycocyamine from the kidney. The storage of nitrogen after methyl testosterone would appear to be in the muscles.

#### SUMMARY

When methyl testosterone was administered orally to normal men or

women on a low creatine diet, the rise in plasma levels of creatine was low during the first ten days, but increased rapidly during the second ten days, exceeding the renal threshold and producing creatinuria.

If creatine were ingested or if plasma creatine levels were high due to renal disease the marked rise in plasma levels occurred sooner after beginning ingestion of the steroid. This is interpreted as indicating there is a limited capacity for storage of creatine in the tissues which can be filled by creatine from any source.

Increased creatinemia and creatinuria followed administration of methyl testosterone to patients with severe hepatic disease.

The effect of methyl testosterone on creatine formation was observed in nephrosis and mild nephritis, but was abolished in severe nephritis. It would seem that the kidney is the primary site of action or that it supplies an essential precursor to some other tissue.

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# AN EVALUATION OF THE GUTERMAN PREGNANCY TEST IN CLINICAL PRACTICE<sup>1</sup>

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THE evaluation of the Guterman pregnancy test here reported has two distinct features: In the first place, we have resisted the temptation to modify the technique and have used it as described by its sponsor (4, 5). Secondly, we have employed the procedure routinely and have avoided a "test-series" of cases. The selection of patients has been entirely in the hands of the house and attending staffs; when it was clinically necessary to determine whether or not a patient was pregnant by laboratory methods, this test was performed, although a Friedman test would also be carried out on request. By this means we have gained a more accurate estimate of the usefulness of the test for hospital and dispensary practice.

The technique outlined by Guterman employs the color reaction of Talbot *et al.* (9) and a modification of the extraction method of Astwood and Jones (1). Essentially it amounts to a qualitative reading of a quantitative change, and is based on the assumption that amenorrhea plus 1 mg. pregnandiol per 100 cc. urine occurs only with pregnancy and always with pregnancy. This assumption has been questioned on a quantitative basis since the isolation of pregnandiol (2, 6, 7), but the qualitative reading (*i.e.*, positive or negative) based on the color reaction had not been suggested before, and merits consideration.

The reading of the test as recommended by Guterman was on the basis of the presence of an orange or yellow-orange color as determined by the naked eye (5). In our effort to maintain the original technique, the tests recorded here were read in this manner. With the appearance of a degree of error, however, the question immediately arises: Are the technicians reading the color change correctly? If so, the source of error lies in the test; if not, it lies in our own reading of the test.

In an effort to answer this question, we have checked the interpretations in about one-third of the cases by photoelectric colorimeter. After having been read and recorded, the sulfuric acid solution was transferred to another laboratory where it was checked colorimetrically by a different technician who was kept in ignorance of the original reading.

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The 420 filter of the Evelyn photoelectric colorimeter was used, and a standard was prepared using 2 gm. of potassium dichromate per 100 cc. distilled water. With 10 cc. of this in a tube the galvanometer was set at 100. The sulfuric acid test solution was then substituted for the standard, and the galvanometer scale read directly. We have not attempted to translate these readings into quantitative terms, and will not so report them for three reasons: 1, the method of extraction is not complete enough to remove all urinary impurities, and the final color intensity is not dependent entirely on the amount of pregnandiol present; 2, the claim made for the procedure was that of qualitative accuracy, and it would gain nothing to criticize it on strict quantitative grounds; 3, our sole purpose in this "spot checking" was to assure ourselves that the tests were being interpreted accurately and that the source of error did not lie in our own personnel.

Our conclusions were as follows:

1. There is a wide color range in the final specimens. With this particular (optional) standard, solutions were encountered that deflected the needle off the scale at the right (less color than the standard, definitely negative) as well as to the left (strongly positive).
2. No test which had been reported *positive* had a reading in the same range as the *negative* tests.
3. The experienced technician can read the presence of the color accurately, and does not represent an appreciable source of error (an error of zero in the tests checked).

### RESULTS

One hundred and thirty-one tests were performed. The follow-up in each case was made not by other pregnancy tests, but by the clinical outcome of the case. One patient could not be located for such follow-up, and the analyses reported here are based on 130 tests. Seventy-one of these patients were pregnant, and in these a *positive* test was obtained in 60 or 84.5 per cent. Fifty-nine cases were not pregnant, and 30 of these (50.8 per cent) had *negative* tests. These gross results must be corrected, however. At the onset of the series, the test was misunderstood by the house staff, and included in the early cases are nine patients who were having some vaginal bleeding. In view of the statement that it requires a *positive* test **plus amenorrhea** to make a diagnosis (4), these results must be ruled out. It must also be immediately acknowledged that a test which is not accurate in the face of vaginal bleeding is of restricted value as a diagnostic aid in hospital practice. These nine results were distributed as follows:

Pregnant with <i>positive</i> test	1
Not pregnant with <i>negative</i> test	1
Not pregnant with <i>positive</i> test	7

In reviewing the records of these patients we noted that in four cases progesterone therapy was started before the test-specimen was collected. In view of the fact that we have obtained *positive* tests in males given two 10 mg. doses of progesterone the day before the morning urine was collected, these cases must also be eliminated. All of these four patients who received progesterone had positive tests; three were pregnant and one was not pregnant.

The corrected results are shown in Table 1. It can be seen from this that the test achieved its greatest accuracy in the presence of pregnancy (83.6

TABLE 1

Pregnant	
Test positive	83.6 per cent
Test negative	16.4 per cent
Not Pregnant	
Test positive	42 per cent
Test negative	58 per cent

per cent correct). In Table 2 the results are rearranged to provide the clinician with more information. Given either a *positive* or a *negative* report by the laboratory, there is approximately a 25 per cent chance of error in diagnosis. It should also be noted that only one of the eleven pregnant patients who had negative tests either aborted or threatened to abort, limiting the prognostic value of this procedure and casting some doubt on the diagnosis of "potential abortion" based on the results of such a determination.

TABLE 2

Positive Test	
Patient pregnant	72.3 per cent
Patient not pregnant	27.7 per cent
Negative Test	
Patient pregnant	27.5 per cent
Patient not pregnant	72.5 per cent

## DISCUSSION

There need be little comment on the usefulness of a test carrying this margin of error. Unfortunately, even if it is assumed that 50 per cent of this error is attributable to the performance of the test in this particular laboratory, it would still not be a procedure of sufficient accuracy for clinical adoption. While a rapid chemical determination for the diagnosis of pregnancy would be of tremendous value clinically (3), the variations in pregnandiol metabolism (7, 8) make it doubtful that an analysis of its excretion, whether qualitative or quantitative, will provide us with such a test.

## CONCLUSIONS

1. The Guterman test was applied to 130 patients in hospital and outpatient practice when a laboratory test for pregnancy was indicated. A hand-picked "test-series" of cases was avoided.

2. The elimination of all patients who are having vaginal bleeding and any who may have received progesterone therapy limits the value of the test in routine hospital diagnostic use.

3. Both the *positive* and the *negative* report were subject to an error of about 25 per cent.

4. The color reaction is definite and can be read by an experienced technician. The source of error apparently lies not in the interpretation of the color reaction but in individual variations in the metabolism of progesterone, both in the pregnant and the non-pregnant woman.

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# THE RELATIONSHIP BETWEEN BLOOD SUGAR AND LYMPHOCYTE LEVELS IN NORMAL INDIVIDUALS

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IN PREVIOUS investigations it has been our experience that in the majority of cases the sugar tolerance of subjects afflicted with mental disturbances is decreased as compared with that of normal subjects (4). In view of the relationship of the adrenal cortex hormone to sugar metabolism (5) it has been suspected that differences in the rate of adrenal discharge may play a part in determining these differences in the reaction to ingested sugar. Since adreno-cortical activity is reflected by the level of the absolute lymphocyte count (1) a study was made of normal subjects in whom simultaneous observations were made of the blood sugar levels and the absolute lymphocyte counts during the course of responses to ingested glucose.

A group of 21 normal subjects was studied, of whom 19 were males. These included university students and personnel of the hospital and were presumably free of any organic illness.

The routine Exton-Rose procedure (3) was followed, the glucose being given in two, 50 gram doses at half-hour intervals. The blood lymphocyte counts and blood sugar levels were measured before each dose of sugar and 30 minutes after the second. Two of the influential variables that have to be controlled in such studies are the effect of nervous tension on glucose tolerance and that of stress (6) on the lymphocyte count. Accordingly, in the first nine subjects a control day was utilized to permit an evaluation of the psychological factors incident to the test or the water administration attendant upon it. On this day, the subjects were given, at 30 minute intervals, two doses 0.06 gm. of saccharin dissolved in 275 cc. of water. Lymphocyte counts and blood sugar measurements were made before each dose of saccharin solution, 30 minutes after the second dose and again 75 minutes later. On a second day, the same procedure was repeated, except that 50 gm. of glucose in 275 cc. of water was ingested instead of saccharin. In the other 12 subjects the usual routine of the two-dose, one-hour test was followed without any control day.

The blood sugar was measured in venous blood by the Folin-Wu technique (macro-alkaline tartrate) with the addition of using a photoelectric

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colorimeter. The absolute lymphocyte count was measured from arterial blood obtained from the ear, the technic used being that described in a previous publication (2).

The results of the test on the first nine subjects are shown in Fig. 1. On the day in which saccharin is administered the blood sugars remain at a stationary level. The lymphocytes show a slight increase (200 cells) from the 30-minute to the 60-minute point and remain at that level for the next 75 minutes. This increase may represent a random variation or may be a special case of the slight upward trend which is found in normal subjects as the day progresses (2).

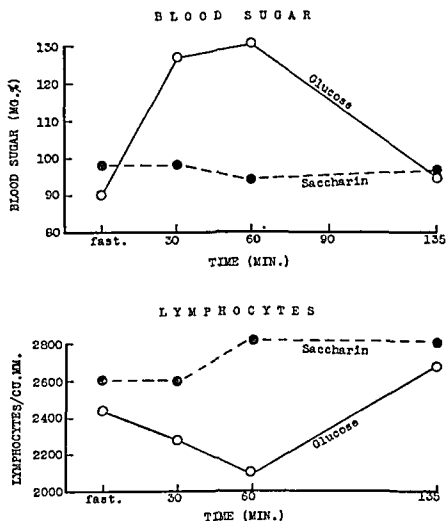


FIG. 1. Means of blood sugar and absolute lymphocyte counts obtained during the course of Exton-Rose glucose tolerance tests compared with values obtained on control days in which saccharin was administered. Nine normal subjects.

On the day in which glucose is administered, the blood sugar rises from 90 to 127 mg. per cent in the first half hour, increases to 131 mg. per cent in the second half hour and then falls to 95 mg. per cent in the next 1½ hour. The tendency to a slight upward trend in the second half hour is probably due to the fact that the subjects may have been under some tension, which factor we have found to cause an elevation of the one hour values (4).

The lymphocyte count shows a trend converse to that of the blood sugar. The values fall at the 30 minute and 60 minute points as the blood



sugar rises and increase subsequently as the blood sugar falls. Thus the mean trends for blood sugar and blood lymphocytes are mirror images of each other. The variation in each one is beyond the range obtained during the day in which saccharin is administered. It is evident, therefore, that neither psychological factors nor water administration caused any significant variation in the blood-sugar or the lymphocyte count.

The mean values for the entire group of 21 subjects (Fig. 2) show the same inverse relationship. The sharp increase in blood sugar obtained 30

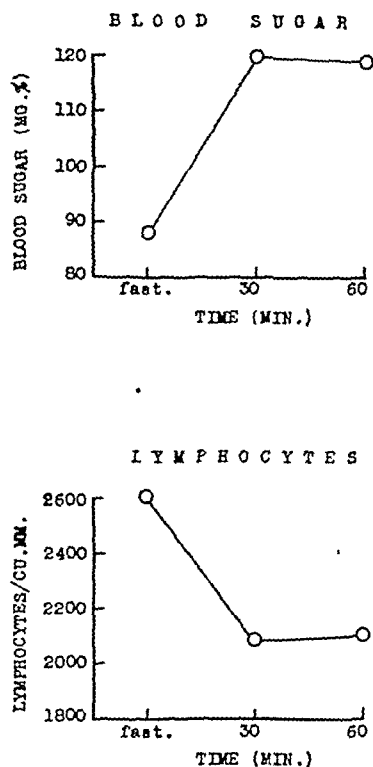


FIG. 2. Means of blood sugar and absolute lymphocyte counts obtained during the course of Exton-Rose glucose tolerance tests in 21 normal subjects.

minutes after the ingestion of 50 gm. of glucose from a fasting value of 88 mg. per cent to 120 mg. per cent is accompanied by a rapid decrease in blood lymphocytes from an initial level of 2611 per cu. mm. to 2078 per cu. mm. In the second half hour of the test, the mean blood sugar remains essentially unchanged and correspondingly so does the lymphocyte count.

In order to determine whether the individual subjects all showed the high relationship between the blood sugar values and the lymphocyte counts displayed by the mean values, a statistical study was made of the absolute changes in the blood sugar in relation to the absolute changes in the blood sugar in each individual for the first and the second half-

hour of the test. Figure 3 shows the results. In the upper figure (A) is charted the difference between the fasting and 30 minute values in blood sugar as compared with the corresponding change in blood lymphocytes. Each circle represents an individual. All the subjects showed an increase in blood sugar but in the case of one individual it was very slight. Fourteen

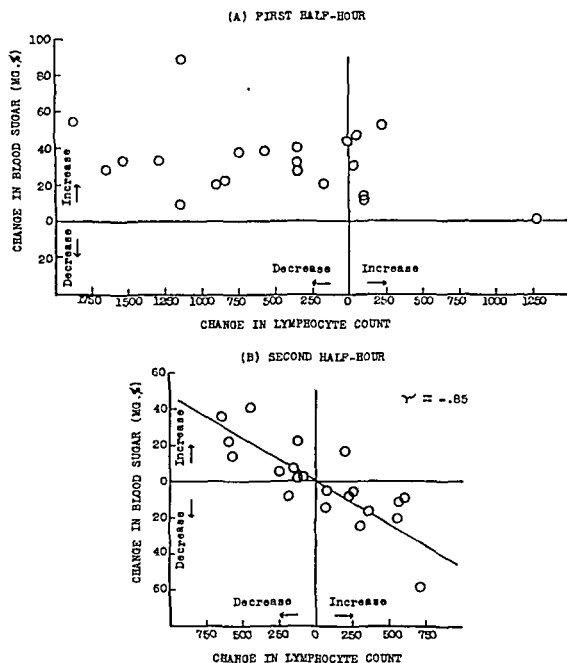


FIG. 3. Scatter diagrams illustrating the relationship between the absolute changes in blood sugar and in lymphocyte levels within each of 21 normal subjects during (A) the first half hour; and (B) the second half hour of the Exton-Rose glucose tolerance test.

of the subjects showed a decrease in lymphocytes, one showed no change and six showed an increase. The trend, of course, is in the direction indicated by the mean values in Figure 2. It is interesting, however, that there is no apparent relationship, quantitatively, between the amount of change in the blood sugar and in the lymphocyte count. Thus, although the mean values show an excellent inverse correlation between the two factors, individually the variation in one bears little relationship to the variation in the other.

On the other hand, the figure in the lower half (B) representing the changes in the second half hour shows a definite relationship between the two factors. It is evident here why the mean trends of Figure 2 are flat since the group shows upward and downward tendencies in blood sugar in about equal amounts. In this case, increases in blood sugar are accompanied by decreases in lymphocytes and *vice versa*. The correlation coefficient is  $-0.85$ , which is about as high as one could expect in biological covariation. An analysis of the average change in the lymphocytes compared with the average change in the blood sugar shows that for each 16.5 mg. per cent change in blood sugar there is a corresponding variation of 340 lymphocytes. It is possible that the increase in the relationship between the blood sugar and the lymphocyte levels in the second half-hour as compared with that of the first half-hour may be indicative of a delay in the homeostatic mechanism controlling these factors so that for at least 30 minutes the variations in the two processes are not geared to each other.

In order to determine more accurately the relationship of the lymphocytic to the glycemic changes, we have divided the subjects arbitrarily into two groups: those having a downward trend in the blood sugar at the 60 minute point and those having an upward trend at this same point. The mean values for the blood sugar and lymphocyte values in the two groups are shown in Figure 4. The group with the downward trend in blood sugar (which numbers 11) shows the typical normal reaction to the ingested glucose. The others (10 in number) show an abnormal trend in the second half-hour. Why this trend is present is as yet obscure. We have found that normal glucose trends can be converted to abnormal ones, *i.e.*, reduced tolerances, under psychological stresses (4). A confirmation of this fact is that a reduced tolerance to glucose is the usual trend in mentally disturbed subjects (4). From the psychological side, "mental tension" seems to be a possible factor in the production of such high blood sugar values (4). On the physiological side, variation in the gastrointestinal absorptive rate does not seem to play a role since the increase in blood sugar for the first 30 minutes is essentially the same in both groups. The other factors are as yet unknown.

The trends in the lymphocytes differ in the two groups of subjects. In the first group (those with a downward tendency in blood sugar) there is a marked fall in lymphocytes in the first 30 minutes and a secondary moderate rise. In the second group, there is a mild fall in lymphocytes in the first half hour, approximately 25 per cent as marked as that of the first group, and a secondary drop in the second 30 minutes. The total fall for the whole hour in lymphocytes in this group is less than that shown by the first group for the first half hour. The trends in the lymphocytes are of course mirror images of the glucose values but the difference in reaction

quantitatively is of interest since, despite the fact that the blood sugar rises are practically identical for the first 30 minutes, the lymphopenic reaction is much milder in the second group.

### DISCUSSION

The data presented above show a definite inverse relationship between the levels of blood sugar and the absolute lymphocyte count. The course

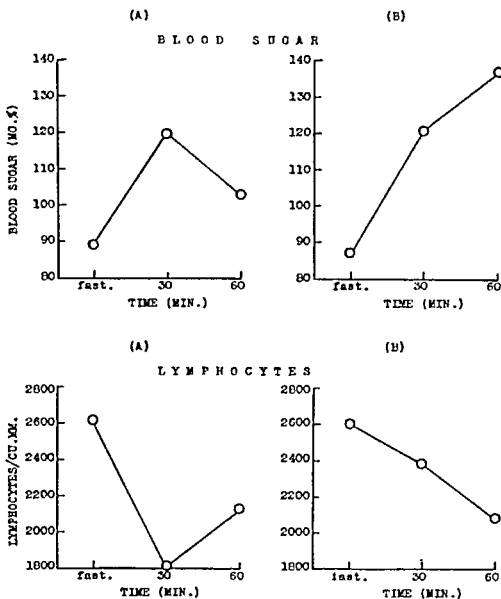


FIG. 4. Means of blood sugar and lymphocyte values obtained during the course of Exton-Rose glucose tolerance tests in 21 normal subjects divided into two groups: (A) those showing "normal" tolerance trends (11), and (B) those showing "reduced" tolerance trends (10).

of this relationship is obscure primarily because the factors controlling the shape of the glucose-tolerance trends are not definitely understood. It may be assumed that the ingestion of glucose imposes a physiological stress upon the organism. Adreno-cortical hormone is then discharged and results in a decrease in the lymphocyte count. When the blood sugar level falls, as in the second half hour of the first group (Fig. 4), adrenocortical activity

ceases and the absolute lymphocyte count rises. If the blood-sugar level continues to rise as in the second half-hour of the second group (Fig. 4), adreno-cortical activity continues and the lymphocyte count continues its fall.

The exact reasons for the lesser fall in lymphocytes in the group with the decreased tolerances are not as yet known. It is possible that the emotional tension which seems to accompany this type of tolerance curve may have already activated the adrenal cortex and to some extent caused an exhaustion phenomenon so that a lesser degree of lymphopenia results. Further speculation in the light of our small knowledge is not justified.

### SUMMARY

1. A study was made of the blood sugar and absolute lymphocyte levels in 21 normal subjects subjected to glucose tolerance tests (Exton-Rose technic).

2. The mean values for the group showed that as the blood sugar rose the lymphocytes decreased in number and *vice versa*.

3. In the first 30 minutes of the test, the change in the blood sugar bore little relationship to the change in the lymphocyte count within each individual.

4. In the second 30 minutes of the test, the change in the blood sugar bore a high relationship (inverse) to the change in the lymphocyte count within each individual. The correlation coefficient was  $-0.85$ .

5. The 10 subjects who showed a somewhat reduced glucose tolerance exhibited a lesser change in the lymphocyte count than did the 11 subjects with a normal glucose tolerance.

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# FURTHER STUDIES ON THE CONTROL OF MENORRHAGIA

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THE successful approach to the management of menorrhagia is clouded by the vast number of therapeutic measures advocated in the past. Their number is legion and runs the gamut from the speculative administration of various drugs and endocrine preparations to the *coup de grace* of the fatalist; to wit, hysterectomy. During the past decade the literature concerned with the organic therapy of functional uterine bleeding has been extensive and the promulgated methods have ranged from the administration of the time honored remedy of extract of ergot to the use of snake venom (37), vitamin B therapy (4), thyroid, the various gonadotrophic preparations, blood from lactating women (13, 14), prolactin (11, 19, 30) and, finally, any one of the various sex sterols, either singly or in combination. Inasmuch as our present knowledge of menstruation implies that it is directly under the control of the steroid hormones of the ovary, it is logical to assume that therapeutic measures to correct excessive uterine bleeding should involve the judicious use of these same steroids. So much may be accomplished with organotherapy of this nature that possible salvage of the patient may be attained without the need for surgical intervention.

The following study, which extended over a period of several years, represents an analysis of our cases of functional uterine bleeding treated by various methods utilizing steroid hormones. A comparison of the therapeutic and physiologic action of the different preparations will be outlined. In addition, a method utilizing the combined administration of testosterone propionate and progesterone will be discussed and presented as the procedure of choice. The concomitant use of these steroids has led to a rapid and efficient method of control of uterine hemorrhage on the basis of arrest of bleeding according to plan (18).

## MATERIALS AND METHODS<sup>2</sup>

Various steroid preparations were administered to several series of patients during their phase of functional uterine bleeding. No attempt was

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<sup>2</sup> The testosterone propionate (*Neo-Hombreol*), progesterone (*Progestin*) and estradiol benzoate (*Dimenformon Benzoate*) used in this study were supplied by Roche Organon, Inc., Nutley, N. J. through the courtesy of Dr. B. J. Brent.

made to control the menorrhagia by any surgical procedure prior to the commencement of endocrine therapy. In the present series the following steroid hormones were employed parenterally: estradiol benzoate, progesterone, and testosterone propionate were administered singly; progesterone, in combination with either estradiol benzoate or testosterone propionate, was also employed. In addition, reference is made to our previous experiences in the therapy of functional uterine bleeding in which we implanted pellets of testosterone (15) and orally administered progesterone and anhydrohydroxyprogesterone (17, 18). Endometrial studies were made throughout this study before and after hormonal therapy when feasible in many of the patients studied.

### RESULTS AND DISCUSSION

**Estrogen.** Many investigators are of the opinion that estrogens are contraindicated in the therapy of menometrorrhagia. Some authors believe that estrogens are not only valueless but that their use is not physiologic, since most cases of functional uterine bleeding show an hyperplastic endometrium (8, 35). On the other hand, there are many adherents to the use of estrogens in the control of uterine hemorrhage (6, 20, 28, 36). The hemostatic action of the injected steroid is thought to be an ovarian negating effect *via* inhibition of pituitary gonadotrophic hormone. It has also been suggested that the administration of exogenous estrogen controls functional uterine bleeding by raising the blood estrogen level above the so-called bleeding level (28). It has been reported that bleeding, when controlled by estrogens, will stop in an average of 4.4 days after the administration of the hormone (6).

In a previous series of cases, estrogens in the form of estradiol benzoate or dipropionate were administered in doses of from 1.66 mg. to 10.0 mg. during the phase of functional uterine bleeding. Massive doses of estrogen frequently stopped the uterine hemorrhage. However, six to ten days after cessation of therapy uterine hemorrhage recurred, and this was observed to be associated with cystic glandular hyperplasia of the endometrium. Thus, although hemostasis was adequately accomplished by the use of estrogenic substances, the subsequent withdrawal bleeding often resulted in a uterine hemorrhage as profuse as the initial episode. The prevention of estrogen withdrawal bleeding by gradual reduction in the amount of hormone administered is indeed a tedious process and still does not give the assurance that estrogen withdrawal bleeding, profuse in nature, will not ensue. It must be emphasized, however, that estrogens do have a definite place in the control of functional uterine bleeding.

**Progesterone.** Progesterone has been advocated and successfully used in the control of functional uterine bleeding (2, 3, 5, 7, 9, 18, 22, 25, 26, 27, 34, 42, 43). The rationale for the administration of this steroid is based on the evidence of progesterone deficiency or persistent estrogenic endometrium in most instances of functional uterine bleeding (23). Progesterone it has been postulated, controls bleeding by the induction of a more normal state of estrogen metabolism (40). Progesterone will prevent estrogen withdrawal bleeding when administered in sufficiently high doses and will lead to a complete breakdown and sloughing of the estrogenic hyperplastic endometrium. On the basis of this it has been suggested that the withdrawal bleeding following progesterone therapy achieves the same result as a surgical curettage, and may be regarded in effect as a "medical curettage" (2). It must be emphasized that the progesterone withdrawal bleeding should not be mistaken for a prolongation or resumption of the menorrhagic syndrome but should be designated as arrest of bleeding according to plan.

Arrest of bleeding according to plan may be defined as follows: When progesterone preparations are administered for periods of from three to five successive days, either parenterally in doses of from 5 mg. to 10 mg. daily, or orally in the form of anhydrohydroxyprogesterone in doses of from 100 mg. to 150 mg. during a period of functional uterine bleeding, hemorrhage may cease, slow down or continue unabated during therapy (18). About two or three days after withdrawal of medication the bleeding suddenly may increase, continue for three or four days and then may stop abruptly or taper down and halt slowly. In all, uterine bleeding continues for six to ten days after cessation of therapy and closely resembles that of a normal menstrual period. Moreover, this latter phase will be succeeded by the desired period of amenorrhea. Unless this phenomenon, "arrest of bleeding according to plan" is appreciated, the clinician may conclude that progesterone therapy increases bleeding and accordingly is contraindicated (16).

Progesterone, on the other hand, has been placed in disrepute by a number of clinicians for the treatment of functional uterine bleeding because upon its withdrawal further bleeding ensues (22) and because its beneficial effect cannot be adequately explained (28). In addition, it has been argued that progesterone actually induces bleeding (20), since inter-menstrual bleeding may be induced on the 14th day if progesterone is administered on the 7th day through the 11th day of the menstrual cycle (44, 45). The bleeding, however, is not excessive and can be labelled as bleeding according to plan which normally ensues after progesterone therapy has been



given. Furthermore, it should be understood that progesterone does not cause bleeding when it is administered during a phase of active progestational activity, as in the post-ovulatory phase or during pregnancy (44, 45). Thus the bleeding observed after the withdrawal of progesterone therapy

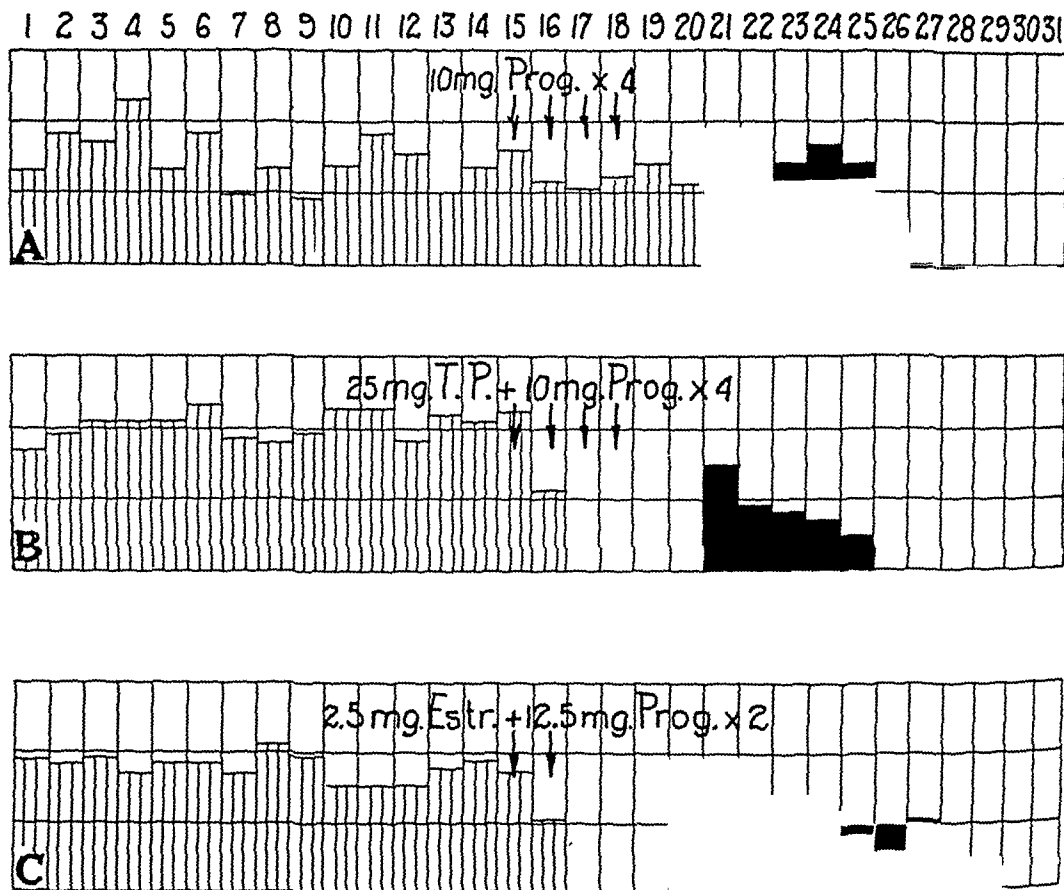


FIG. 1. Diagrammatic presentation showing effect of therapy with various steroid hormones in functional uterine bleeding.

A. Therapy = 10 mg. progesterone for four consecutive days.

B. Therapy = 25 mg. testosterone propionate administered concomitantly with 10 mg. of progesterone for four consecutive days.

C. Therapy = 2.5 mg. estradiol benzoate administered concomitantly with 12.5 mg. progesterone for two consecutive days.

Striped zone represents bout of menorrhagia.

Solid zone represents period of withdrawal bleeding.

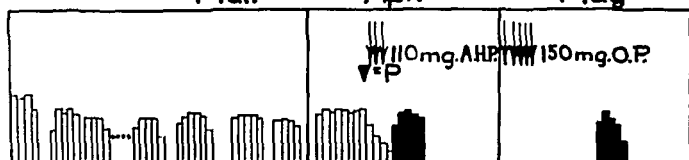
is not analogous to that observed in menometrorrhagia but simulates the normal physiologic menstruation and will cease in a period of time approximating that of a normal menstrual period.

The general effect of administration of progesterone parenterally upon functional uterine bleeding is graphically presented in Figure 1a. As stated

above, bleeding may not be controlled during progesterone therapy. Upon discontinuation of progesterone an increase in amount of bleeding may occur but complete stoppage within six to ten days after the last progesterone injection is the usual result. Thus arrest of bleeding according to plan has occurred.

Miss F. - w.f. 17 - Menorrhagia - Bleeding off and on for 4 months. D&C several months previously without benefit.

Mar. Apr. May



Miss B - w.f. 15 - Menorrhagia 5 weeks steadily.

July Aug. Sept.

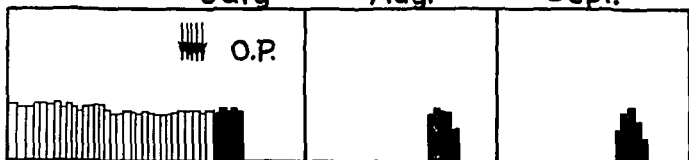


FIG. 2

▽ = Suction curettage  
P = Progesterinal endometrium  
↓↓ = Days of administration of hormone  
AHP = Anhydrohydroxyprogesterone  
OP = Oral progesterone (linguet form)

The results observed with oral progesterone and anhydrohydroxyprogesterone have been described in previous reports (17, 18). However, three typical cases are depicted in Figures 2 and 3 where one may note that either anhydrohydroxyprogesterone or progesterone administered orally has an ameliorating effect upon the functional bleeding. Complete salvage was obtained in most instances. In several, pregnancy followed soon there-

after (Fig. 3). The average dose of progesterone employed when administered alone (parenterally) has been 10 mg. given daily for a period of from three to five days. Of 35 patients treated with parenteral or oral preparations of progesterone, 90 per cent responded in the typical pattern depicted below.

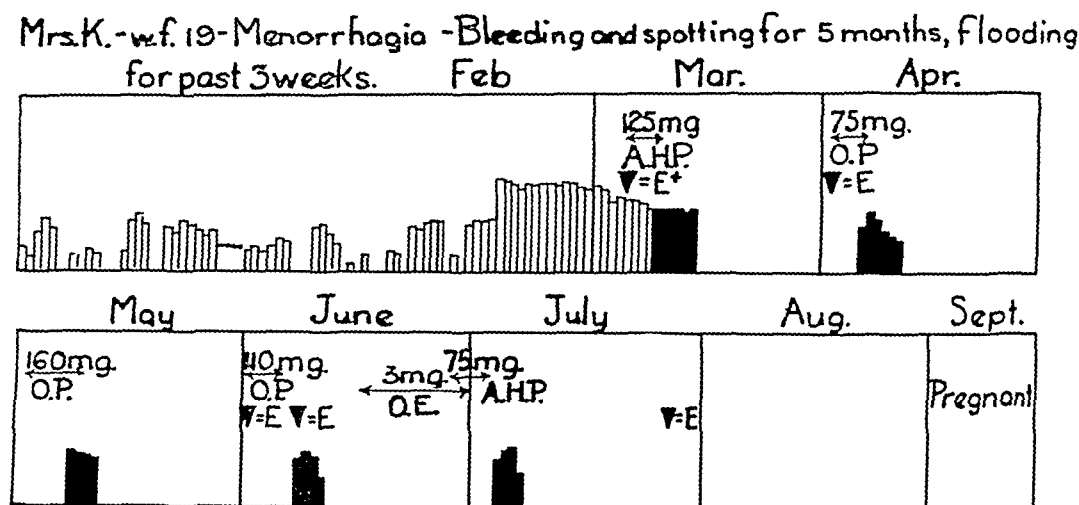


FIG. 3

$\nabla$  = Suction curettage  
 $E^+$  = Cystic glandular hyperplasia  
 $E$  = Estrogenic endometrium  
 AHP = Anhydrohydroxyprogesterone  
 OP = Oral progesterone (linguet form)  
 OE = Estradiol (oral)

**Testosterone.** The therapeutic value of testosterone in menometrorrhagia (1, 10, 15, 33, 38, 41) has been ascribed to the following properties of the androgen: 1, estrogen neutralization (39); 2, inhibition of the pituitary gonadotrophic complex (10); 3, myometrial effects (1), which are: a, inhibition of myometrial contractions; b, stimulation of growth of myometrial elements.

The estrogen inhibiting effect of testosterone, as has been suggested (39), cannot withstand the modern concept of the physiologic action of androgenic and estrogenic substances. The nullifying effect of testosterone on the function of the female reproductive tract must be attributed to the secondary effects following the suppression of the hypophyseal gonadotrophic hormones. The mucifying action of androgens on the vaginal mucosa of the rat (39) is not due to the estrogen negating effect of testosterone but to the primary effect of the androgen on the reproductive system of the female rat (29). In addition we have noticed that estrogen

## INFLUENCE OF PELLET IMPLANTATION ON ENDOMETRIUM

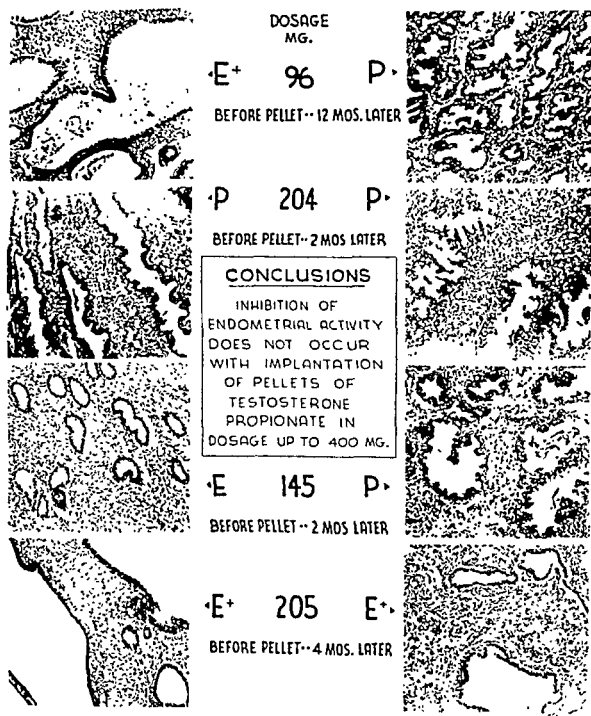


FIG. 4. Endometrium before and after androgen therapy in a selected group of patients in whom functional uterine bleeding was successfully controlled.

applied topically to the pigmentation spot of the golden hamster in no way influences the stimulating action of simultaneously applied androgen upon the production of pigmentation and pellage changes (31, 32).

The clinical improvement following pellet implantation of testosterone in cases of functional uterine bleeding and metrorrhagia associated with uterine fibroids could not be ascribed to a pituitary inhibiting effect of the sterol. Ovarian function, as mirrored by endometrial studies, in most instances was unaltered since the endometrium was maintained in es-

essentially the same *status quo* as that observed prior to implantation of the pellet, despite the resulting clinical improvement (15). Evidence from some cases implied that androgens in moderate but adequate dosage did not inhibit endometrial activity (Figure 4). In fact, cyclic bleeding from a secretory endometrium followed not infrequently.

We, too, are inclined to believe that the myometrial action of testosterone is the paramount effect of this steroid in controlling functional uterine bleeding (1, 15). Administration of daily doses of 25 mg. of testosterone propionate for four to six days has been of value in controlling menorrhagia. Approximately 50 per cent of our cases have benefited by such a regimen. One of the inadequacies of androgen therapy is that ultimate salvage is comparatively infrequent (15). Others have also reported that the effect of androgens on the endometrium is variable and not predictable (1, 41).

**Estrogen and progesterone.** The combined use of these two sterols in a form of cyclic therapy has been employed in the treatment of functional uterine bleeding (23, 24). Their use is based upon the fact that estrogen and progesterone synergize one another in their action upon the endometrium. Their combined hemostatic effect, it may be reasoned, will achieve an effect that neither one could satisfactorily accomplish alone. The regulatory effects of cyclic estrogen and progesterone therapy upon the untoward uterine bleeding has been ascribed to the estrogen employed while the return of the ovulatory cycles has been attributed to the synergism present between estrogen and progesterone and their effect upon the pituitary gonadotrophic complex (21, 23).

In our series of patients we have made daily concomitant injections of 2.5 mg. of estradiol benzoate and 12.5 mg. of progesterone<sup>3</sup> for a two day period as opposed to the cyclic method of administration of these steroids. The concomitant use of an estrogen and progesterone as a simplified procedure for the treatment of amenorrhea has been successfully employed (12, 46) but has not been applied to the therapy of menometrorrhagia. A summary of our composite results is diagrammatically presented in Fig. 1c. This plan differs from the cyclic mode of therapy in having a shorter period of treatment. With this procedure, cessation of bleeding usually occurs within the second day after initiation of therapy. Withdrawal bleeding follows after an interval of three or four days. The flow may continue for a period of six to ten days, with the metrostaxis in the latter half of the period being only slight in extent. Thus in contrast to progesterone alone, immediate bleeding is more quickly controlled. Amenorrhea follows the

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<sup>3</sup> *Di-Pro Ampules*, containing 2.5 mg. *Dimenformon Benzoate* and 12.5 mg. *Progesterin* were kindly furnished by Roche Organon, Inc.

withdrawal bleeding (arrest of bleeding according to plan) and persists for at least the duration of one normal menstrual period.

**Testosterone propionate and progesterone.** On the basis of the improvement in functional uterine bleeding achieved by the use of either androgens or progesterone alone, it was decided to incorporate the myometrial action of testosterone and the endometrial influencing effect of progesterone in a

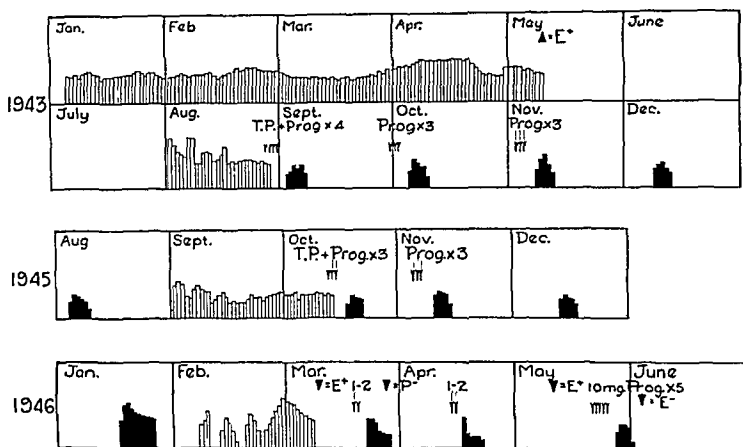


FIG. 5

$\Delta$  = D and C

$\nabla$  = Suction curettage

E<sup>+</sup> = Cystic glandular hyperplasia

E<sup>-</sup> = Hypoestrogenic endometrium

P = Imperfect progestinal or mixed endometrium

↓ T.P. + Prog = 25. mg. testosterone propionate and 10 mg. progesterone combined therapy

↓ 1-2 = 2.5 mg. estradiol benzoate administered concomitantly with 12.5 mg. progesterone for 2 consecutive days

(Note that dilatation and curettage performed in May, 1943, controlled bleeding for only 2½ months.)

combined form of therapy. The testosterone propionate was employed for its hemostatic propensities upon the uterus while progesterone was incorporated to induce desquamation of an hyperplastic or malfunctioning endometrium. The presumptive advantage of an androgen over that of a estrogen is that theoretically the former does not induce further hyperplasia

of the endometrium. The more obvious advantage is that combined androgen-progesterone therapy affords a "breathing spell" to the patient between the immediate arrest of bleeding and the subsequent withdrawal bleeding.

The mode of therapy that has been followed in this regimen consists of three to five consecutive daily injections of combined doses of 25 mg. of testosterone propionate and 10 mg. of progesterone. When these substances are administered during a bout of menstrual hemorrhage, bleeding is frequently controlled on the first to second day of therapy, and at times hemostasis may be observed within six to eight hours after the initial injection. The period of amenorrhea then persists for two to four days, and is subsequently followed by withdrawal bleeding. This latter flow may continue for four to six days and is less in extent than that observed after the use of progesterone alone or progesterone and estrogens (Figs. 1b and c). The results in a patient treated in this manner are diagrammatically presented in Figure 5. Here it may be noted that combined testosterone-progesterone therapy was first used with excellent clinical results in September, 1943, and again in October, 1945. The prompt control of bleeding is noteworthy. The incorporation of testosterone propionate with progesterone significantly lessens the extent and duration of progesterone withdrawal bleeding.

After the control of the siege of functional bleeding, subsequent salvage of the patient may depend upon continuing the same form of therapy at monthly intervals until resumption of normal menstrual cycles may be attained. Progesterone has proved to be most valuable and is administered for three or four days in daily doses of 10 mg. each about 21-30 days after bleeding has been controlled. If the withdrawal bleeding following these prophylactic measures is excessive, 25 mg. of testosterone propionate may be incorporated with the progesterone to reduce the amount of flow observed after cessation of progesterone therapy. After several monthly courses of such therapy the patient is then observed for evidence of either recurrence of her functional uterine hemorrhage or the re-establishment of physiologic menstrual cycles. If there is a resumption of the former, further therapy must be instigated. In our hands we have found the combined androgen-progestin mode of therapy to yield the most promising results from the point of view of immediate hemostasis and subsequent salvage of the patient afflicted with functional uterine bleeding.<sup>4</sup>

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<sup>4</sup> In a few patients a short period of bleeding has occurred 4-7 days after cessation of the withdrawal bleeding. The bleeding was usually scanty and lasted only a few days. The physiological basis for this phenomenon is, at present, obscure.

## SUMMARY

1. The examination of the endometrium soon after the arrest of menorrhagia by estrogenic therapy usually reveals an hyperplastic or a proliferative endometrium.

2. When moderate doses of androgenic therapy are employed and bleeding is arrested, the endometrium is maintained apparently in the same status as prior to therapy.

3. When progesterone therapy is used and bleeding is arrested "according to plan," i.e., about seven to ten days after cessation of therapy, shedding of the endometrium frequently occurs, comparable to that which is observed in normal physiologic menstruation. However, the loss of blood during the seven to ten day period may be excessive.

4. The administration of 25 mg. of testosterone propionate and 10 mg. of progesterone daily during a four to five day period results in a rapid cessation of bleeding, which after an interval of four or five days is followed by a short bout of withdrawal bleeding.

5. In the study of functional uterine bleeding, extending over a period of many years, this method of therapy has thus far proved the most promising and ideal in the management of menorrhagia.

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# PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

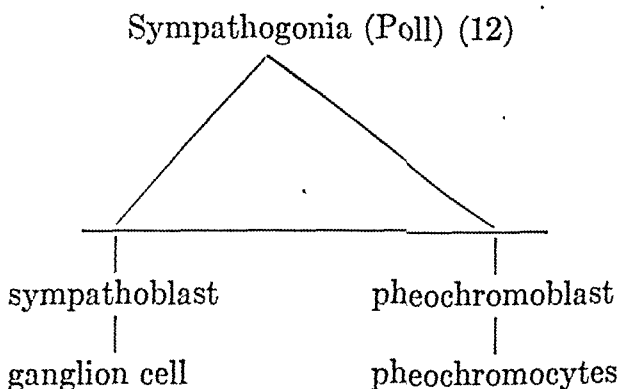
Its Role in the Pathogenesis of a Malignant Hypertension

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## INTRODUCTION

**T**UMORS of the pheochromic cell arising in the adrenal medulla and producing a well established hormonal symptom-complex are occasionally encountered. The pheochromocyte or the cell of origin of this tumor is the result of differentiation of the sympathogonia or sympathetic formative cells into two systems, the future ganglion cell (nervous) and the pheochromocyte (endocrine). Sympathicoblastoma, neuroblastoma and ganglioneuroma are tumors arising in the ganglion cells in various stages of its maturation (13). They are non-hormonal and produce only signs and symptoms referable to the formation of a mass with pressure on surrounding structures. They are usually malignant and occur in infancy or early childhood (10). The pheochromocytoma arises from mature cells which have differentiated from the primitive sympathogonia to form the endocrine portion of the adrenal medulla.



The differentiation usually takes place during late fetal development and may not be complete until the time of puberty (14). The mother cells or sympathogonia are small with scanty cytoplasm and a round, deeply staining nucleus with well developed chromatin. The pheochromocytes are much larger with irregular cytoplasm which stains palely and contains many small basophilic granules. The nucleus is vesicular and ovoid with a

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prominent nucleolus. The pheochromocyte possesses the characteristic property of staining brown with chromic salts. Abnormal proliferation of the pheochromocytes or the mature cells of the endocrine series gives rise to the tumors of the adrenal medulla variously named chromaffinoma, paraganglioma or pheochromocytoma. They arise not only in the adrenal medulla but may occur wherever chromaffin tissue is present, principally the carotid body, the aortic bodies, the organ of Zuckerkandl, the sacrococcygeal region and in the retroperitoneal tissues (8). Usually they are benign tumors which remain localized, although there are on record 12 cases in which malignant transformation has been observed. When the tumor becomes malignant, the characteristic clinical symptom-complex is usually absent (9).

The tumors usually occur in adults with the peak incidence in the fifth decade. It is predominantly a disease of the white race as only 2 of 121 reported cases have occurred in Negroes.

Beer, King, and Prinzmetal (1) first demonstrated that the symptomatology was due to the presence in the blood of a pressor substance which was similar in its actions to epinephrine. Others have since supported this finding and identified the substance as epinephrine (8).

In 35 instances surgical excision of the tumor has been reported and was successfully accomplished in 27. In all, removal of the tumor resulted in complete alleviation of symptoms and there has been none in which a permanent hypertension has resulted.

The present case was considered significant because of the presence of a severe necrotizing arteriolitis in many organs of the body. Death was the result of surgical shock with no clinical manifestations of uremia. It was also unusual because of the presence of the typical clinical symptoms of the adrenal-sympathetic syndrome in association with malignant transformations in the tumor.

#### REPORT OF CASE

*L. K.* (Barnes Hospital, St. Louis, Mo., #109286), a 26 year old, white laborer, was admitted to Barnes Hospital on November 11, 1943 and died November 24, 1943.

**Chief complaints:** The patient complained of frequent attacks of severe headaches, blurring of vision, precordial distress and vomiting. He had also noticed swelling of his ankles and weight loss of 15 pounds.

**Family history:** His mother had high blood pressure for a number of years.

**Past history:** The patient was in good health until the present illness. He had been employed as a laborer for several years and was accustomed to hard work. He used no tobacco or alcohol, and no drugs other than an occasional laxative. Except for incidental injuries, he recalled no medical attention. His accustomed weight was 200 pounds. In December, 1942, he fell from a tractor and struck his head and right shoulder. He was treated in a local hospital where he remained for five or six days, but did not return to work until three weeks later. During his stay in the hospital nothing was mentioned of the presence of high blood pressure and he presumed no abnormalities were found.

**Present illness:** In April, 1943, he suddenly began to vomit dark green material. There was no associated nausea, but the attacks of vomiting occurred as frequently as five or six times a day. There were no other symptoms at this time. He was sent by his physician to a hospital for examination where he was told he had high blood pressure. The vomiting persisted and the patient developed severe frontal and later occipital headaches which frequently preceded the vomiting. The headaches occurred almost daily. Later the same month he awakened one morning with markedly impaired vision in the left eye which slowly improved. The right eye was unaffected. The patient had numerous nose bleeds and gingival bleeding on several occasions during his illness. Three weeks prior to his admission to Barnes Hospital he coughed up a considerable amount of dark red blood; this was unassociated with chest pain. At this time he also complained of his heart beating rapidly and vigorously. He noticed swelling of his ankles on several occasions. The patient had nocturia five or six times a night at the onset of his illness, but at the time of admission to Barnes Hospital this had ceased. He was told by his physician, however, that he had blood and albumin in his urine. During attacks the patient had noticed that his extremities would become cold and pale and then hot and flushed followed by profuse sweating. During the period of his illness he had lost 15 pounds. He became irritable and there was progressive weakness of his extremities. An accompanying letter from the patient's physician stated that during the last two months he had been given sodium thiocyanate.

**Physical examination:** The patient's temperature was 37° C, the pulse rate was 90 beats per minute, respirations 24 per minute, and the blood pressure was 200/150 mm. of Hg. He appeared chronically ill and the skin was pale except for some flushing of the cheeks. The eyes were normal to external examination. Ophthalmoscopic examination showed recent hemorrhages at the margin of the optic discs. The gums were bleeding. The nasopharynx was normal. There was slight diminution of breath sounds over the right side of the chest anteriorly, but no other abnormalities were noted. The heart beat was forceful and thrusting with visual and tactile pulsations. The heart was enlarged to the left and there was a palpable thrill at the base. The cardiac rhythm was regular. A soft systolic murmur was heard over the mitral area and the aortic second sound was somewhat accentuated. There was some voluntary resistance to deep palpation in both kidney regions, but no definite masses were noted. The prostate was small, firm and not tender. There was no edema of the extremities. Neurologic examination was negative.

**Laboratory data:** The red blood cell count was 4.53 million per cubic millimeter and the hemoglobin 14.2 grams. The white blood cell count was 18,600 and the differential showed 2 basophils, 1 eosinophil, 5 stabs, 68 segmented forms, 20 lymphocytes and 4 monocytes. Examination of the urine at the time of admission showed a specific gravity of 1.011, 4+ albumin, occasional red blood cells, a few white blood cells and rare hyaline and granular casts. The Kahn reaction of the blood was negative. Examination of the stool was negative. The fasting blood sugar was 127 mg. per cent and the non-protein nitrogen of the blood was 17 mg. per cent. The total serum protein was 7.2 grams with 5.2 grams of albumin and 2.0 grams of globulin. Urine cultures showed no growth. Roentgenograms of the chest showed a focus of pulmonary infiltration at the level of the third and fourth ribs on the right. The superior margin of this region was sharply margined and a diagnosis of "probable bronchopneumonia of the middle lobe of the right lung" was made. A barium enema was performed and reported as "indeterminate." An electrocardiogram taken shortly after admission showed "myocardial damage."

**Course in the hospital:** Consultation with the Department of Urology was obtained

and cystoscopic examination was performed. Examination of the urine from the right and left ureters showed 2+ albumin. There was delayed appearance of the phenosulphophthalein after intravenous injection. Intravenous pyelograms showed delayed function of both kidneys. Retrograde pyelograms showed medial rotation and downward displacement of the right kidney. The daily variations in blood pressure and pulse are shown in the accompanying chart. Repeated examinations of the urine showed persistent albuminuria and the presence of many casts. The specific gravity of the urine varied between 1.010 and 1.020. Because of the downward displacement of the right kidney and the clinical symptoms of paroxysmal hypertension a diagnosis of pheochromocytoma of the right adrenal gland was made. It was decided, in spite of the relatively unsatisfactory condition of the patient, surgical excision of the tumor should be attempted.<sup>1</sup> On November 24, on the thirteenth hospital day, a right lumbar incision was made from the 12th rib to the crest of the ileum. The right kidney was exposed and was found to be displaced anteriorly and downward and rotated medially. An attempt was made to explore the right adrenal gland, but when blunt dissection was attempted in this region, the patient's blood pressure fell precipitously and became unobtainable. Emergency measures consisting of stimulants, adrenal cortical extract and oxygen were administered. Exploration was discontinued and the abdomen was closed. The patient failed to respond to emergency treatment, the blood pressure was not obtainable and he expired 2½ hours after the induction of anesthesia. He was given a total of 2,000 cc. of 5 per cent glucose in saline immediately before and during the operation.

**Autopsy.** Washington University Department of Pathology, # 10892. Post mortem examination was performed one hour after death. There was a recent operative wound of the right lumbar region and a moderate amount of hemorrhage into the retroperitoneal tissues. The right kidney was displaced inferiorly and rotated medially by a large tumor which had partially replaced the right adrenal gland. The tumor was surrounded by a connective tissue capsule which also inclosed the remaining adrenal tissue. The total weight of the tumor and adrenal gland was 413 grams. Cut section of the tumor showed grayish brown tissue which was soft, friable, and contained numerous small yellow foci of necrosis. A small unguled portion of adrenal cortex was present near the posterior margin of the tumor. No extension of the tumor through its capsule was found but it had invaded the right adrenal vein and extended into the inferior vena cava. Careful examination of the regional lymph nodes showed no gross involvement by tumor.

The weight of the kidneys was increased, the left weighing 240 grams and the right 210 grams. The surfaces were smooth and cut sections showed a normal relative thickness of the cortex and medulla. In the mucosa of the renal pelvis there were numerous small hemorrhages, the largest measuring 12 millimeters in diameter.

The heart was greatly increased in size, weighing 630 gm. The pericardium was smooth and no deposits of fibrin were present on the surfaces. The myocardium of the left ventricle measured 18 mm. in diameter while that of the right ventricle measured 5 mm. The myocardium of the interventricular septum was reddish brown and contained no foci of fibrosis. The endocardium and the valves of the heart were normal. The coronary arteries contained a few elevated yellow plaques on the intimal surface. Beneath the intima of the pulmonary artery 1.5 cm. above the pulmonic valve, there was a small focus of hemorrhage measuring 8 mm. × 2 mm.

<sup>1</sup> The operation was performed by Dr. Peter Heinbecker to whom we are indebted for permission to report this case.

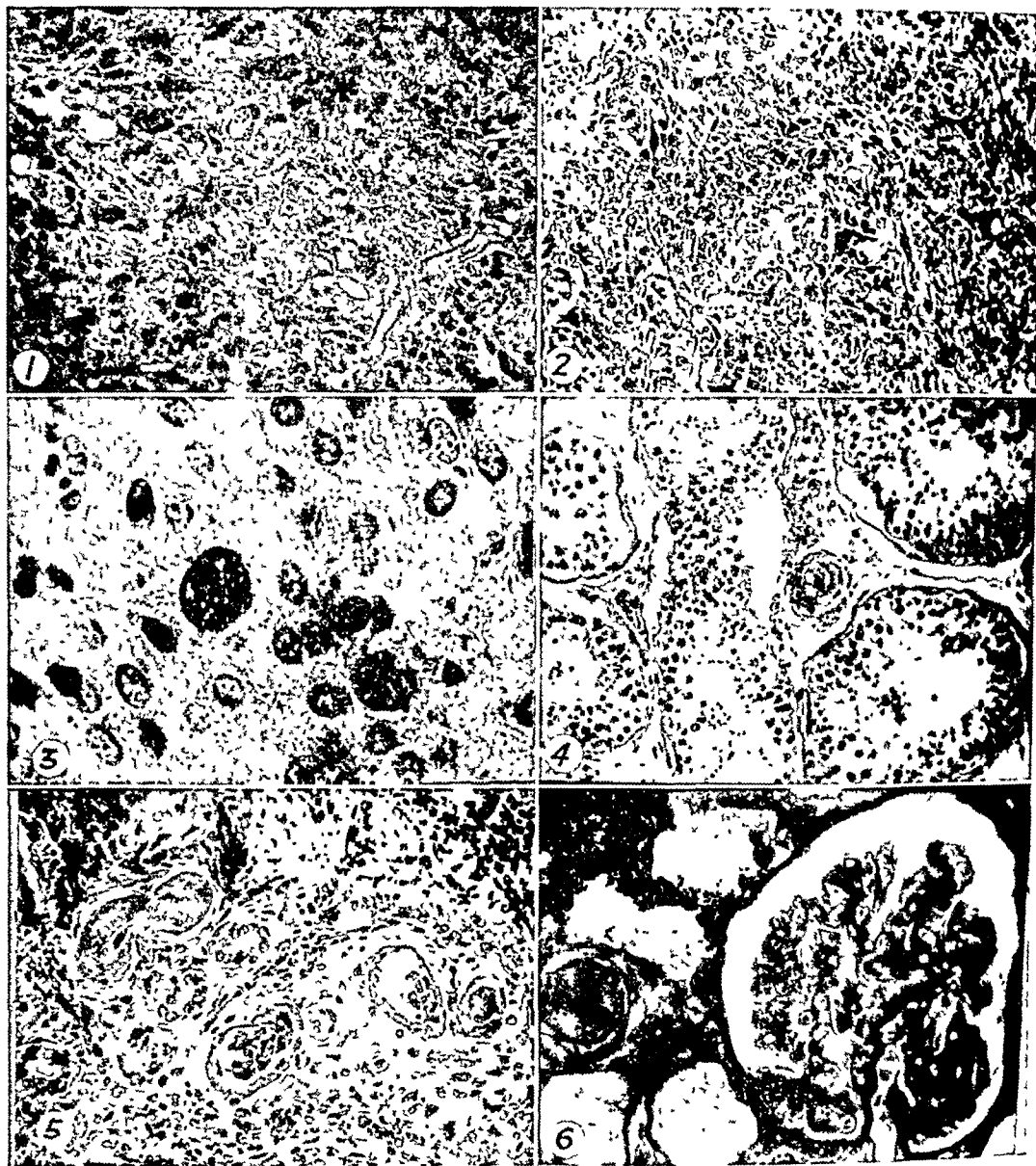


FIG. 1. Primary tumor showing pleomorphism of the cellular pattern and presence of numerous multinucleated cells. Hematoxylin eosin stain ( $\times 570$ ).

FIG. 2. Primary tumor showing tendency toward fibrillar pattern. Multinucleated cells are also conspicuous. Hematoxylin eosin stain ( $\times 500$ ).

FIG. 3. Eosinophilic body within the cytoplasm of a large tumor cell. The vesicular nuclei with well developed chromatin material and the granular cytoplasm are well shown. Hematoxylin eosin stain ( $\times 1100$ ).

FIG. 4. Small arteriole within the interstitium of the testis showing hemorrhage within the wall and early necrosis. Hematoxylin eosin stain ( $\times 570$ ).

FIG. 5. Several small renal arterioles near the corticomedullary junction. The extensive necrosis of the arteriolar wall is well shown with disappearance of a nuclei and

The lower lobes of the lungs contained a few small infarcts, the largest measuring 1 centimeter in diameter.

The other viscera contained no significant gross pathologic changes.

**Microscopic examination:** Blocks taken from various parts of the tumor were fixed in Zenker-formalin and in formaldehyde. Paraffin sections stained with hematoxylin-eosin and Goldner's modification of Masson's trichrome stain were examined.

The tumor consisted of large polyhedral cells which were irregular in shape and varied from 10 to 25 microns in diameter (Fig. 1). The cytoplasm was finely granular and varied in its affinity for hematoxylin, some cells staining deeply while others were only slightly basophilic. The nuclei were large and usually round although some were irregular. The chromatin network was dense and stained deeply. There was usually a prominent nucleolus. Numerous multinucleated cells were diffusely scattered throughout the tumor (Figs. 1 and 2). They contained from 3 to 8 nuclei which were hyperchromatic. The cytoplasm was abundant and stained deeply with eosin. Within the cytoplasm and occasionally within the nuclei of many of the cells were small ovoid bodies which had a homogeneous, hyaline appearance and were deeply eosinophilic (Fig. 3). Numerous mitotic figures were seen throughout the sections of tumor. In some regions the tumor cells appeared to be radially arranged around blood vessels. There were a few foci of necrosis within the tumor.

Sections of the kidneys showed increased amounts of connective tissue in both the cortex and the medulla. There was slight fibrous thickening of the peripheral layer of Bowman's capsule and of the basement membrane of the glomerular capillaries (Fig. 6). The proximal convoluted tubules were large and the epithelium was swollen. The lumina of many were filled with a granular eosinophilic substance. The cytoplasm of the tubular epithelium contained numerous eosinophilic granules and hyaline droplets. In a few of the tubules there was necrosis of the epithelium. The most striking pathologic changes in the kidneys were in the blood vessels, particularly the small arteries and arterioles. All of the arterioles observed in the sections of kidney showed marked thickening of the walls which consisted of hyalination of the media and hyperplasia of the intima. Many of the arterioles had undergone necrosis (Figs. 4 and 5). The changes in the large arteries consisted almost entirely of medial thickening and hyalination. There was very little intimal proliferation in these vessels in contrast to that seen in the arterioles. In the medulla there was slight increase in fibrous connective tissue between the tubules but the architecture was well preserved.

Sections of the pancreas showed an increase in the interlobular and interacinar connective tissue. The arterioles within the substance of the pancreas showed thickening of their walls and many had undergone necrosis. The same type of arteriolar change was present as observed in the kidney, consisting primarily of hyalination of the media and slight intimal proliferation. In some arterioles the necrosis was so extensive that the entire circumference of the wall was destroyed and the lumen was filled with necrotic material (Fig. 5).

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granularity of the cytoplasm. Goldner's modification of Masson's trichrome stain ( $\times 570$ ).

FIG. 6. Glomerulus showing minimal fibrosis of the basement membrane and of the peripheral layer of Bowman's capsule. There is no visible thickening of the efferent arteriole. In the adjacent small arteriole the nuclei have disappeared and there is necrosis of the wall with almost complete disappearance of the lumen. Goldner's modification of Masson's trichrome stain ( $\times 570$ ).



Sections of the liver showed slight dilatation of the sinusoids, particularly in the region of the central veins and congestion with red blood cells. There was no increase in the amount of periportal connective tissue. An occasional hepatic cell contained large vacuoles of fat. This fatty change was most extensive near the central veins. A few of the hepatic nuclei were vacuolated and appeared to contain glycogen.

The spleen showed evidence of passive congestion but no other pathologic changes.

Sections of skeletal muscle showed thickening of the arterioles and hyalination of the media with very little intimal proliferation. All of the arterioles in the sections of skeletal muscle showed such changes. The muscle fibers were normal.

There was slight hyperplasia of the cells of the left adrenal medulla and marked thickening of the arterioles, a few of which were necrotic. The changes in these vessels consisted primarily of medial thickening and hyalination without intimal hyperplasia. The left adrenal cortex was normal.

The lungs showed evidence of a slight passive congestion. The arterioles within the lungs did not show any of the changes observed in the other organs. There was slight atelectasis and many of the alveoli contained large macrophages which were filled with yellow-brown pigment.

**Final anatomic diagnosis:** Pheochromocytoma of the right adrenal (413 gm.) with partial displacement and rotation of the right kidney and with partial flattening of the upper pole of the right kidney; extension of pheochromocytoma through right suprarenal vein into the inferior vena cava; arteriolar sclerosis with necrosis of the arteriolar walls, generalized; hypertrophy and dilatation of the heart, 630 gm. (history of hypertension for 7 months); interstitial fibrosis of the pancreas; fibrosis of the islets of Langerhans, slight; recent wound of right flank (history of exploratory operation, 2½ hours); hemorrhage into the retroperitoneal tissue in the region of the right kidney; hemorrhage into the mucosa of the renal pelvis; hemorrhage into the wall of the pulmonary artery; infarcts of the lungs, small; fatty metamorphosis of the liver, slight; hyaline droplets in the renal tubules.

#### BIO-ASSAY OF TUMOR

An extract of the tumor was prepared by the method of Folin, Cannon and Denis (5) with slight variations. Fifteen gm. of fresh tumor tissue were ground in a mortar with an abrasive and 20 cc. of 0.1 N HCl. This mixture was rinsed into an Erlenmeyer flask with 10 cc. of 0.1 N HCl and 100 cc. of distilled water and heated to boiling. To the boiling mixture was added 10 cc. of a 10 per cent sodium acetate solution and the mixture reheated to boiling. The mixture was transferred to a flask and 200 cc. of distilled water added. It was then centrifuged and the clear extract was withdrawn for physiologic tests.

A dog was prepared with ether anesthesia which was administered through a tracheal tube. A cannula was inserted into the right common carotid artery and into the femoral vein. An elastic band was placed around the thorax of the dog. Tracings of the pressure within the carotid artery and the femoral vein and of the respirations were made on a revolving kymograph. The injection of 2 cc. of the extract prepared from the tumor caused a sharp rise in blood pressure which persisted for 120 seconds be-

fore it gradually descended to the normal level. The resulting curve was nearly identical with that produced by 0.15 cc. of 1:1000 solution of epinephrine.<sup>2</sup> The vasopressor effect of the extract and of the solution of epinephrine was not elicited after the injection of 10 mg. of ergotoxine.

From these data it may be concluded that the tumor removed from this patient contained a substance which had a vasopressor effect on the dog analogous to that produced by epinephrine. The vasopressor effect of the extract of tumor and of the epinephrine could be prevented by the previous injection of ergotoxine.

#### DISCUSSION

The onset of illness in this case was typical of the paroxysms which have been observed in previously reported instances of pheochromocytoma of the adrenal gland. However, the subsequent development of permanent hypertension is unusual in patients with this disease. The demonstration of a vasopressor substance in the tumor which had an action on the blood pressure of the dog similar to that of epinephrine affords a possible explanation for the subsequent development of permanent hypertension. Goldblatt (6) has shown that elevation of the blood pressure of dogs over a period of time produces generalized thickening of the arterioles which may be responsible for the resulting permanent hypertension. The changes observed in the arterioles are comparable to those seen in man with essential hypertension. The effect of long standing vasoconstriction produced by a humoral mechanism such as epinephrine has not been thoroughly studied. Pearce and Stanton (11) have observed changes in the arteries and arterioles of rabbits subjected to repeated injections of epinephrine. The lesions were confined for the most part to the large arteries although thickening of the walls of the small arterioles was observed. The absence of any previous kidney disease or hypertension in this patient affords evidence that in the human subject the presence of large amounts of vasopressor substance in the blood over a period of time may produce arteriolar lesions which result in permanent hypertension.

The subsequent development of a malignant phase of hypertension without associated renal insufficiency is unusual. The observations of Goldblatt (7) have demonstrated that at least two factors, hypertension (mechanical factor) and uremia (humoral factor), must be present for the production of the malignant phase of hypertension and the typical pathologic changes of necrosis of the arterioles and associated hemorrhages. Dogs with a severe hypertension for as long as five years without signs of renal insufficiency or uremia did not show the clinical or pathologic changes of

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<sup>2</sup> Parke, Davis and Company, Detroit, Michigan.

malignant hypertension. From this observation he concluded that elevation of the blood pressure alone, even to high levels for long periods of time, was not sufficient to produce the malignant phase of hypertension. Animals which did not have hypertension but which died of uremia, produced by the removal of both kidneys, likewise did not show the generalized hyalination and necrosis of the arterioles with associated hemorrhages in other organs. This showed conclusively that the accumulation of the chemical substances in the blood associated with azotemia of renal origin was not sufficient to produce the pathologic changes associated with malignant hypertension. However, dogs with hypertension which subsequently developed renal insufficiency and uremia showed necrotic arterioles and hemorrhages. That the lesions were not due to ischemia is evidenced by the absence of necrotizing changes in the arterioles of the kidney distal to the clamp. This demonstration of the pathogenesis of malignant hypertension affords the most adequate explanation of this condition in patients with hypertension of renal origin. However, it is not entirely applicable to this case because of the absence of one of the essential factors, uremia.

Wilson and Pickering (15) concluded that severe hypertension alone was sufficient to produce intimal hyperplasia and necrosis of the arterioles in the rabbit. They believed that renal insufficiency played no part in the process but based this conclusion on the absence of structural changes in the kidney and not on chemical determinations for the accumulation of the products of nitrogen metabolism in the blood. Histologic examination alone is apparently not sufficient evidence for the presence or absence of renal insufficiency.

Necrotizing arteriolar changes have not been produced in experimental animals by the injection of large amounts of epinephrine. However, in the absence of azotemia of either renal or extrarenal origin, the liberation of large amounts of pressor substance in an individual with essential hypertension may be sufficient to produce the pathologic changes of malignant hypertension. There have been no reports of the effects of injecting large amounts of epinephrine into an experimental animal with hypertension. The extremely high bursting blood pressure may under these circumstances be sufficient to produce arteriolar necrosis and associated hemorrhages without the accumulation of nitrogenous products in the blood.

Some degree of renal damage was present at the time of admission to the hospital as evidence by the presence of albumin, casts and red and white blood cells in the urine. However, the nonprotein nitrogen of the blood was 17 mgm. per cent so that there was no clinical evidence of renal insufficiency. The pathologic lesions observed microscopically in the kidneys consisted of thickening of all of the arterioles with necrosis and a

slight degree of parenchymatous degeneration of the tubular epithelium. The glomeruli showed only a slight increase in the amount of connective tissue in Bowman's capsule and in the basement membrane of the capillaries. The pathologic evidence indicated conclusively that the patient was not suffering from chronic renal disease before the onset of symptoms referable to the adrenal tumor. Hence from these observations and the previously cited evidence that the presence of large amounts of vasopressor substances in the blood may produce changes in the arterioles which result in permanent hypertension, the continued release of this substance after the development of permanent hypertension is apparently sufficient to produce the pathologic changes associated with malignant hypertension without insufficiency.

McGavack, Benjamin, Speer and Klotz (9) studied the reported cases of malignant pheochromocytoma and found that those with widespread metastases did not present the clinical features seen in patients with the benign form of the tumor. In two cases actual hypotension was present and in none was there hypertension. They have established the criteria for denoting malignancy as the actual presence of metastases which were not present in this case. However, the extension and growth of the tumor into the inferior vena cava seems to us to be sufficient evidence upon which to make a diagnosis of malignancy. The fact that distant metastases, particularly in the lungs, had not occurred seems to be a matter of chance as all the predisposing factors were present. Certainly from the clinical standpoint the tumor was malignant as invasion and extension into the inferior vena cava made complete surgical removal all but impossible.

We have been able to find twelve cases in which the authors considered the tumors to be malignant. Braster and Keith (2) and Evans and Stewart (4) report two cases in which the typical adrenal-sympathetic syndrome was present and the tumors were considered malignant by the authors. In each instance there were local invasive tendencies without distant metastasis. These cases do not fulfill the criteria established by McGavack, Benjamin, Speer, and Klotz for malignancy. However, we believe that sufficient evidence is available in this case to classify the pheochromocytoma as malignant and that it presents the unusual combination of the adrenal-sympathetic syndrome in association with malignant transformation in the tumor.

#### SUMMARY

A case of pheochromocytoma of the adrenal medulla is presented. The onset of the illness was typical consisting of attacks of vomiting, headache, flushing of the face, blurring of vision and paroxysmal hypertension. The hypertension subsequently became permanent, and shortly after attempted

removal of the tumor the patient died without clinical evidence of uremia. The unusual features were the pathologic finding of a widespread necrosis of the arterioles and associated hemorrhages without evidence of uremia, and of malignant transformation in the tumor characterized by invasion of the right adrenal vein and of the inferior vena cava. Epinephrine-like substance was demonstrated in the tumor.

It is postulated that the prolonged discharge of vasopressor substance from the tumor may produce changes in the arterioles which result in permanent hypertension. The continued release of this substance after the development of a permanent elevation of the blood pressure may be responsible for the production of arteriolar necrosis and hemorrhages without the presence of uremia.

Although the tumor had undergone malignant transformation, the typical hormone symptom-complex was present.

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# Letter to the Editor

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TO THE EDITOR:

## PROGESTERONE THERAPY OF UTERINE FIBROMYOMAS

**F**IBROMYOMAS have been produced in the guinea pig by estrogenic therapy. This phenomenon has been studied extensively by Lipschütz,<sup>1</sup> who demonstrated further that certain steroids would not only prevent formation of experimental fibromyomas but also cause regression of fibromyomas despite continued estrogenic therapy. Progesterone was by far the most effective of these steroids.

We have attempted to evaluate the effects of progesterone therapy on human uterine fibromyomas. Because it is not possible to determine small changes in size of a uterine tumor by bimanual examination alone, we have employed roentgenography with intrauterine instillation of radiopaque oil and interperitoneal injection of carbon dioxide or either of the two alone. Great care has been taken to duplicate the procedure as exactly as possible in successive studies on the same patient.

It seems apparent that if progesterone is to have a beneficial effect on human uterine fibromyomas, it will most likely be in patients who are still menstruating regularly. The three patients who are the subjects of this communication were selected because: 1, they had uterine fibromyomas which could be well outlined by one or both of our roentgenographic procedures; 2, they were menstruating regularly; 3, they were cooperative enough to permit thorough and repeated study; and 4, each understood that it was imperative to have a hysterectomy immediately after the conclusion of the therapeutic and diagnostic studies.

In addition to the effect of progesterone on the size of the fibromyomas, we observed its effects on the urinary excretion of gonadotrophic hormones and 17-ketosteroids and the histologic picture of the endometrium and mammary gland. However, this communication is concerned only with the effects on the size of the fibromyomas.

Three patients were given daily intramuscular injections of 20 mg. of progesterone in 2 cc. of peanut oil. The progesterone was administered for 39, 61 and 47 days respectively.

The therapy produced no change in the size of the fibromyomas. The

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<sup>1</sup> LIPSCHUTZ, A. Induction and Prevention of Abdominal Fibroids by Steroid Hormones, and Their Bearing on Growth and Development. *Cold Spring Harbor Symposium on Quantitative Biology* 10: 79-89 (1942).

size and contour at removal were as expected from the roentgenograms made with contrast medium.

The purpose of this note is to emphasize the necessity of adequate, controlled observation by objective means before conclusions may be drawn concerning this exceedingly important subject. To illustrate and emphasize this point, we felt that by bimanual examination there was a definite reduction in the size of the fibromyoma in one patient but roentgenograms with contrast medium showed no such change. Furthermore, it is our feeling that until it has been definitely demonstrated that progesterone does have a salutary effect on human uterine fibromyomas, it is essential to complete all studies of the effect of hormonal therapy on uterine tumors by histologic examination.

Our studies are in progress; this note was prompted by the recent report of Goodman<sup>2</sup> in this journal in which he described shrinkage of uterine tumors due to progesterone. His data were entirely subjective. Since objective technics are available, we would emphasize their importance in these studies.

ALBERT SEGALOFF, M.D.

J. C. WEED, M.D.

WILLIAM PARSON, M.D.

July 13, 1946.

*From The Alton Ochsner Medical Foundation, The Ochsner Clinic and the Departments of Medicine and Gynecology, Tulane University of Louisiana School of Medicine, New Orleans.*

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<sup>2</sup> GOODMAN, A. L. Progesterone Therapy in Uterine Fibromyoma. *J. Clin. Endocrinology* 6: 402-408 (May, 1946).



# Association Announcement

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## *Nominations for Awards of the Association*

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. These include the Squibb and Ciba Awards which have been given in the past and a new award which will be known as the Ayerst, McKenna & Harrison Fellowship in Endocrinology, to be given for the first time in 1947. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary. A nomination should be accompanied by a statement of the importance of the nominee's contributions to endocrinology and by a bibliography of his most important papers with reprints if possible. Application forms may be obtained from the secretary and all nominations should be sent to Dr. Henry H. Turner, Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma, not later than March 15, 1947.

### THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of \$1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, in 1942 to Dr. Fred C. Koch, in 1944 to Dr. Edward A. Doisy, in 1945 to Dr. E. C. Kendall, and in 1946 to Dr. Carl G. Hartman. No award was made in 1943. No age or other special limitation is stipulated by the Donor of the Award. So far it has been given for long-continued work of a high quality.

### THE CIBA AWARD

The Ciba Award was established in 1942 and is to be given to an investigator not over 35 years of age. No recipient was selected in 1943. In 1944 the Award was given to Dr. E. B. Astwood, in 1945 to Dr. Jane Anne Russell and in 1946 to Dr. Martin M. Hoffman. The Award is for \$1,200.00. If the recipient chooses to use the Award to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to \$1,800.00.

### THE AYERST, MCKENNA & HARRISON FELLOWSHIP

This award was authorized by the Council at the 1946 meeting in San Francisco and will be presented for the first time at the 1947 annual meeting in Atlantic City. The annual stipend is \$2,500.00 and may be renewed at the discretion of the Committee on Awards. Applicants for this fellowship shall fulfill the following requirements:



1. They must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed requirements for their Ph.D. or M.C.D. degree.
2. They must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals.
3. They must submit a program of proposed study.
4. They must indicate one or more institutions where the proposed program shall be carried out.
5. They must submit statements of approval from the investigators with whom they propose to conduct their research.
6. They must serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

## Association Notice

The 29th annual meeting of the Association for the Study of Internal Secretions will be held Friday and Saturday, June 6th and 7th, 1947, in the Viking Room of Haddon Hall Hotel, Atlantic City, New Jersey, preceding the Centennial meeting of the American Medical Association.

Members are urged to make reservations immediately inasmuch as the hotels expect to be filled to capacity. Make your reservations directly with Chalfonte-Haddon Hall advising them of the accommodations you wish. Rates are as follows:

	Chalfonte	Haddon Hall
Single room with bath:	\$6, \$7, \$9	\$7, \$8, \$10
Double room with bath (without ocean view):	\$8 and \$10	\$10 and \$12
Double room with bath (side ocean view):	\$12	\$14
Double room with bath (ocean front):	\$14 and \$16	\$16 and \$18

Make your reservations now and avoid disappointment—remember, you can always cancel them at a later date.

Those wishing to present papers should send the title of the paper and four copies of a comprehensive abstract to the president, Dr. Fuller Albright, Massachusetts General Hospital, Boston, Massachusetts, at their earliest convenience. Abstracts submitted should be in proper form for printing in the program. Not more than the first two hundred words can be included in the printed abstract.

Further information regarding the meeting will be forthcoming at an early date.

# Abstracts of CURRENT ENDOCRINE LITERATURE

*Editor; D. A. McGINTY. Collaborators; A. R. ABARBANELL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKEIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.*

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## ENDOCRINE GENERAL

LI, C. H., C. KALMAN, H. M. EVANS AND MIRIAM E. SIMPSON. The effect of hypophysectomy and adrenocorticotrophic hormone on the alkaline phosphatase of rat plasma. *J. Biol. Chem.* 163(3): 715-721. (1946).

The bony changes which occur in hypophysectomized rats suggested a study of phosphatase since this enzyme is intimately related to changes in bone. Plasma alkaline phosphatase decreased progressively after hypophysectomy in male and female rats 40 days of age. In normal and hypophysectomized rats, administration of adrenocorticotrophic hormone in doses causing adrenal hypertrophy produced a decrease in the plasma alkaline phosphatase. Since desoxycorticosterone acetate produces an increase and corticosterone a decrease in the phosphatase of rat femurs, it is concluded that adrenals caused to hypertrophy by adrenocorticotrophic hormone secrete mainly, if not wholly, steroids with an oxygen atom on carbon atom no. 11 rather than substances akin to desoxycorticosterone.—H.L.M.

NELSON, MARJORIE M. AND H. M. EVANS. Pantothenic acid deficiency and reproduction in the rat. *J. Nutrition* 31 (4): 497-507 (1946).

The authors studied the effect of purified diets deficient in pantothenic acid on reproduction in normal adult female rats. When the experimental diets were instituted on the 13th day of gestation, no difference was noted between the control and experimental groups as far as the average number of young born and their average weight at birth. When the experimental diets were started on the first day of gestation, one-third of the implantations were resorbed. Also the average weight of the young at birth and the average number of young per litter were decreased. When the experimental diets were started 16-23 days before mating, one-third of the animals failed to have implantations, and 50-100 per cent of the implantations were resorbed. From those animals with implants that were not resorbed, the number of young per litter as well as their average birth weight was decreased. The growth and survival of the young borne by the pantothenic acid deficient mothers were decreased in proportion to the duration of the deficiency. Diets restricted in calories (to 69 per cent of normal intake) with adequate amounts of pantothenic acid did not interfere with reproduction.—H.S.G.

SYDENHAM, A. Amenorrhoea at Stanley Camp, Hong Kong, during internment. *Brit. Med. J.* 2: 159 (1946).

A survey of 655 British women interned in Stanley Camp, seven months after the fall of Hong Kong, showed that 60.5 per cent of the women between the ages of 15 and 45 years were suffering from amenorrhea, 53.67 per cent having had amenorrhea for more than three months. Of the 234 women with amenorrhea all except six had begun menstruating by May 1943. Because of the early development of this wave of amenorrhea, it was felt that emotional shock must have been the primary cause. Other symptoms of dietary deficiency were not obvious at that time.

A second wave of amenorrhea developed in the early months of 1944 when the protein intake was severely lowered by the removal of meat from the diet. Undernutrition was apparently the primary factor at this time. Many of the young women who developed amenorrhea showed a gain in weight of flabby fat while normal individuals were losing weight on the same diet. It was thought, therefore, that thyroid deficiency was also produced.—*L.T.S.*

## PANCREAS

BARBOSA, J. J. DE C., M. B. DOCKERTY AND J. M. WAUGH. Pancreatic heterotopia. Review of the literature and report of 41 authenticated surgical cases, of which 25 were clinically significant. *Surg., Gyn. & Obst.* 82: 527-42 (1946).

Hypoglycemia and hyperinsulinism have been observed in association with heterotopic pancreatic tissue presenting both benign and malignant change in its insular portion. If exploration is being carried out in a case of hypoglycemia with a definite "Whipple's triad" and, after a thorough search, no tumor is found in the pancreas, the surgeon should look for heterotopic pancreatic tissue. The most common locations are the stomach, duodenum and jejunum in that order.—*J.M.*

HAIST, R. E. Carbohydrate metabolism in traumatic shock. *Am. J. Digest. Dis.* 13 (5): 152-155 (1946).

The author observed animals whose hind limbs had been traumatized by pressure cuffs (dogs) and metal clamps (rats), shock being studied when these traumatizing agents were removed. The shocked animals showed high blood sugars and low levels of liver and muscle glycogen. The muscles of the injured extremities contained no detectable glycogen. Glucose administration led to high blood sugars over a prolonged period without affecting the glycogen levels. Insulin lowered the blood sugar but did not increase muscle or liver glycogen. Fructose raised the levels of blood glucose but did not affect the liver glycogen values. The turnover of high energy phosphorus compounds (adenosine triphosphate and phosphocreatine) was normal in the unclamped extremities. The author concluded that, since reclamping reversed most of the changes noted, some change had occurred in the damaged tissue which affected the activity of parts remote from the site of injury.—*H.S.G.*

MIRSKY, I. A. What is the cause of diabetes mellitus in man? *Am. J. Digest. Dis.*, 13 (5): 130-136 (1946).

The roles of pancreatic insufficiency and insulin insufficiency in causing diabetes

mellitus in the human were discussed. The author pointed out that since the pancreas in 25 per cent of diabetics showed no morphologic evidence of damage, pancreatectomy in man led to an insulin requirement much less than that observed in many human diabetics, and since the islets of Langerhans are hyperplastic in cases of acromegaly with diabetes mellitus, the pancreatic insufficiency hypothesis is invalid. However, because there are tissue proteinases or insulin antagonists which may increase the utilization, destruction or inhibition of insulin and thus produce decreased amounts of circulating insulin, the author felt insulin insufficiency to be a more likely cause for diabetes mellitus in humans. The conclusion reached was that the etiology of diabetes mellitus in man is unknown.—*H.S.G.*

MOSENTHAL, H. O. AND EILEEN BARRY. Evaluation of blood sugar tests: Significance of the non-glucose reducing substances and the arterio-venous blood sugar difference. *Am. J. Digest. Dis.* 13 (5): 160-167 (1946).

The difference between the values obtained by the Folin-Wu method of blood sugar determination and the 'the true blood sugar' method of Lauber and Mattice was used as a measure of non-glucose reducing substances in the blood. In 200 cases (normal and diabetic) the non-glucose reducing substances varied from one to 78 mg. per 100 cc. (38 per cent of the cases were above the usually accepted limit of 30 mg. per 100 cc.). When glucose tolerance tests were performed, the non-glucose reducing substances fluctuated markedly and unpredictably. Therefore, the authors concluded that true blood sugars are a better guide in interpreting glucose tolerance. 200 determinations (mostly on diabetics) of arterio-venous blood sugar difference revealed a variation from minus 26 to 102 mg. per 100 cc. Although it has been stated that venous blood sugar is higher than arterial blood sugar in diabetics, this was observed in only nine per cent of the tests. The average arterio-venous blood sugar difference in fasting normals and diabetics was 9 mg. per 100 cc. and this difference was not found to vary in diabetics with or without insulin two hours after a meal. However, the arterio-venous difference increased in both diabetics and non-diabetics after 100 Gms. of glucose was administered. The authors felt that the arterio-venous difference is a measure of sugar metabolized in the forearm, and therefore venous blood samples should be taken to indicate the over-all efficiency of carbohydrate metabolism. It was reasoned that arterial blood samples are preferable to determine renal glycosuria.—*H.S.G.*

PETERS, J. P. The use of carbohydrate in diabetic acidosis. *Am. J. Digest. Dis.*, 13 (5): 127-128 (1946).

The author advocated the intravenous administration of glucose (in addition to insulin) in cases of diabetic acidosis and coma. Reasoning that the high blood sugar (derived from tissue protein and fat) gives an exaggerated impression of the amount of glucose in the body and that the liver is probably deglycogenated in diabetic acidosis, he favored the use of parenteral glucose 1) to compensate for the glucose lost in the urine, 2) to accelerate the synthesis of liver glycogen which he felt is necessary before the patient can burn carbohydrate, and 3) to prevent possible hypoglycemic shock resulting from insulin administration. He treated patients in diabetic acidosis with 25 Gms. of glucose (10 per cent solution) intravenously and 50 units of insulin as soon as they were seen. Then glucose was administered (10 Gms. per hour) until the blood sugar

SYDENHAM, A. Amenorrhoea at Stanley Camp, Hong Kong, during internment. *Brit. Med. J.* 2: 159 (1946).

A survey of 655 British women interned in Stanley Camp, seven months after the fall of Hong Kong, showed that 60.5 per cent of the women between the ages of 15 and 45 years were suffering from amenorrhea, 53.67 per cent having had amenorrhea for more than three months. Of the 234 women with amenorrhea all except six had begun menstruating by May 1943. Because of the early development of this wave of amenorrhea, it was felt that emotional shock must have been the primary cause. Other symptoms of dietary deficiency were not obvious at that time.

A second wave of amenorrhea developed in the early months of 1944 when the protein intake was severely lowered by the removal of meat from the diet. Undernutrition was apparently the primary factor at this time. Many of the young women who developed amenorrhea showed a gain in weight of flabby fat while normal individuals were losing weight on the same diet. It was thought, therefore, that thyroid deficiency was also produced.—*L.T.S.*

## PANCREAS

BARBOSA, J. J. DE C., M. B. DOCKERTY AND J. M. WAUGH. Pancreatic heterotopia. Review of the literature and report of 41 authenticated surgical cases, of which 25 were clinically significant. *Surg., Gyn. & Obst.* 82: 527-42 (1946).

Hypoglycemia and hyperinsulinism have been observed in association with heterotopic pancreatic tissue presenting both benign and malignant change in its insular portion. If exploration is being carried out in a case of hypoglycemia with a definite "Whipple's triad" and, after a thorough search, no tumor is found in the pancreas, the surgeon should look for heterotopic pancreatic tissue. The most common locations are the stomach, duodenum and jejunum in that order.—*J.M.*

HAIST, R. E. Carbohydrate metabolism in traumatic shock. *Am. J. Digest. Dis.* 13 (5): 152-155 (1946).

The author observed animals whose hind limbs had been traumatized by pressure cuffs (dogs) and metal clamps (rats), shock being studied when these traumatizing agents were removed. The shocked animals showed high blood sugars and low levels of liver and muscle glycogen. The muscles of the injured extremities contained no detectable glycogen. Glucose administration led to high blood sugars over a prolonged period without affecting the glycogen levels. Insulin lowered the blood sugar but did not increase muscle or liver glycogen. Fructose raised the levels of blood glucose but did not affect the liver glycogen values. The turnover of high energy phosphorus compounds (adenosine triphosphate and phosphocreatine) was normal in the unclamped extremities. The author concluded that, since reclamping reversed most of the changes noted, some change had occurred in the damaged tissue which affected the activity of parts remote from the site of injury.—*H.S.G.*

MIRSKY, I. A. What is the cause of diabetes mellitus in man? *Am. J. Digest. Dis.*, 13 (5): 130-136 (1946).

The roles of pancreatic insufficiency and insulin insufficiency in causing diabetes

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